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CHEMICAL CONSTITUTION
AND
PHYSIOLOGICAL ACTION

BY

PROF. DR. LEOPOLD SPIEGEL
(BERLIN)

TRANSLATED WITH ADDITIONS
FROM THE GERMAN

BY

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FOREWORD

The action of chemical agents upon the animal organism, and particularly upon man, is of the greatest importance and interest. Far too little has been done toward systematizing our knowledge of this subject, and there is no doubt that this field offers an enormous opportunity for useful research.

The purpose and scope of the present treatise have seemed sufficiently distinct from other works, and of sufficient importance to justify its translation. We have also attempted to bring the work up to date by a consideration of some of the more recent literature.

The borderlands between the formerly distinct sciences are becoming of more and more importance as each science progresses. The relation between chemical constitution and physiological action is of such fundamental and far-reaching significance that a general idea of the work which has already been done should be of interest not only to the physiological chemist and to the searcher for new synthetic therapeutic agents, but also to the physician who must prescribe the use of such compounds. For real, rational scientific medicine must be founded upon a knowledge of this subject, and in order that a steady progress shall be made, a systematic knowledge must replace haphazard and empirical information.

This work is presented with the hope that it may aid not only in the search for new synthetic therapeutic agents, but also in a more thorough understanding of the action and the reasons for the action of many of the compounds which are already in use.

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CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION

GENERAL CONSIDERATIONS

Descriptive chemistry has brought forth an enormous number of chemical compounds, and has showed us their properties. The similarity of certain compounds which could be brought into genetic relationship, if not actually converted one to another, made possible the grouping of such bodies into series. This led to a classification of the chemical elements which directly explained reactions common to all the members of a series. General discrepancies which were observed were explained by assuming not only different valences for the different elements in combination, but also a varying valence for a single element. Finally, the analogies between these series of elements were found to be related to the weight of the hypothetical atoms, and this resulted in the development of hypotheses connecting atomic weights with chemical and physical properties. The most perfect expression of such relations to-day is the periodic system of the elements. There were only timid attempts in the field of inorganic chemistry to explain the properties of compounds by discovering not only the kind and number of atoms in a combination, but also the manner in which they were joined—the constitution of the compounds. The most powerful impulse to this work came from the knowledge of the carbon compounds. For in these bodies a few elements form countless compounds whose properties range from those of a harmless brilliant dye to those of an apparently insignificant but really powerful poison alkaloid. In such a chaotic labyrinth it was impossible to find a path without the Ariadne thread of constitutional interpretation.

Organic chemists were therefore first in this work, systematically propounding and elaborating hypotheses, which were later applied to inorganic compounds.

Real scientific chemistry begins, at least in the organic field, with the determination of the influence of constitution upon the various properties of the compounds.

The primary object of investigation is to ascertain the effect of the inner structure upon chemical and physical phenomena such as chemical reactivity, melting-point, boiling-point, heat of combustion, refractivity, dielectric constant, etc.

Especial interest was early excited by the color of substances and particularly the property of imparting the original or a modified color to animal and plant fibers.

Only in recent times has it been attempted to connect the chemical constitution of compounds with those properties which are most delicate and most important to man—that is, with their effect upon the animal organism.

Of course the idea of finding a connective relation between chemical and physiological properties of compounds is by no means new. This thought naturally arose with the earliest chemical considerations which were directed to substances of especial importance and interest to man, whether their qualities were injurious or remedial. Then appeared the genius of Paracelsus, who directed chemistry into new courses with the significant expression, " The real object of chemistry is not to make gold, but to prepare medicines." (Von Meyer, *History of Chemistry*, 2d ed. from 2d German ed.)

He announced a proposition that has a decided smack of modern times when he said "The healthy human body is a combination of chemical substances; when this suffers any change, diseases arise, which accordingly can be cured only by chemical remedies."

The further advancement we owe next to the Iatro-chemical school, which proceeded along the course which Paracelsus had laid. This school, under de la Boë Sylvius, attempted to make all the science of medicine applied chemistry. The pity is that in this development there sprang up beside really far-reaching and fundamental ideas the most vague and speculative phantasies and imaginings, which could not fail to discredit the whole science of chemistry for some time, particularly so in investigating the curative effects of compounds.

Chemical and physiological knowledge was in too undeveloped a condition for us to expect a great deal of productive work from those times. In order that we may evaluate the effect produced upon life functions by the substances artificially ingested into the organism it is quite necessary, according to our present ideas, that we postulate that these substances enter into reaction with the constituents of the cells which transmit the effect to the whole organism. Then it becomes at once evident to the chemist that such an interaction depends not only upon the structure of the ingested reagent, but quite as much upon the structure of the cell substances.

Thus we arrive at the discouraging conclusion that for a full and complete solution of our problems, for a sure and definite knowledge of the action of foodstuffs, medicines or poisons, it is quite certainly essential that we know the constitution of the cell substance and the significance of this constitution in the various physiological functions. Until this is known we must remain in the dark. At all events to-day, when the chemical constitution of one of the interacting materials—that is, the ingested substance, is known with a probability that borders upon certainty, we are facing our problem with views quite different from those which were current in the days of Paracelsus, Van Helmont and Sylvius. We may even allow ourselves to hope that these very relationships to whose investigation we are here devoted may become a means of assured progress in the determination of the ultimate nature of the cell substances themselves. For the behavior of a substance toward known reagents gives us quite generally a clue to the presence of groups whose reaction characteristics we know.

At any rate if we were to limit ourselves even to-day to our investigation of the actions and effects of only those substances whose constitution may be considered to be wholly and perfectly cleared up in all details, our field would be comparatively small. For we must remember that it is in a series of substances whose constitution has so far defied all attempts at solution where we find some of the physiologically most active material. But there are fortunately many pertinent relationships that can be established even with our very limited knowledge of constitutional structure, just as is the case in pure chemistry. For example, it is not at all necessary to know the structure of aromatic hydrocarbons in order to conclude definitely after noting the varying behavior of their nitro derivatives on the one hand, and the corresponding amines formed by reduction of these nitro bodies on the other hand, as compared with the corresponding diazonium salts, that the amino group on the aromatic nucleus plays an important and especial role in the reactions involved. In the same manner in the case of physiologically active substances we can easily trace the influence of various substitutions, although the actual constitution and occasionally even the empirical composition of the main body of the compound may be entirely unknown to us. In the cases of some substances the living organism is an indicator of such remarkably great delicacy that it far transcends all chemical reagents and reminds us strongly of the sensitiveness of the electroscope in the detection of radioactive substances. For example, the living organism demonstrates most clearly changes of this sort in the formation of specific anti-bodies from the normal components of the animal body. Such changes could not even be surmised by any chemical reagents, although there can be no question that for their fundamental causes they must be referred to alteration of the chemical and stearic structure of complex molecules.

As we have already noted, material ingested from without enters into relationship with the body materials in the performance of the various body functions. In general the more these ingested substances differ from those of the body and the greater the effect observed by the introduction of the most minute quantities, so much the more easily may these relationships be determined. Both of these conditions are well satisfied in the case of those substances which are in part injurious to the body as poisons and in part beneficial as medicines. We shall therefore essentially restrict ourselves to a consideration of these substances in the following treatise.

First of all let us consider what quantities of foreign substance introduced into the body are capable of being recognized by a definite effect. Hydrocyanic acid is fatal for man in doses of 0.05 gm., and its effects are very clearly discernible in doses of 0.0005 gm. Strychnine, which is fatal for adult man in doses of 0.10 gm. to 0.12 gm., shows a very marked effect even in doses of 0.003 gm. Pilocarpine is utilized in a therapeutic way for man in quantities of 0.005 gm. Let us for a moment consider these small quantities to be distributed only in the blood, which in an adult human being is estimated at 5.5 kgm. We then find the following concentrations in the blood for doses that are effective:

Hydrocyanic acid..	1 : 11,000,000
Strychnine..	1 : 1,800,000
Pilocarpine..	1 : 1,100,000

Now for some of the particularly delicate chemical reactions the following limits of sensitiveness have been found:

$AgNO_3$ and HCl...........	1 : 1,000,000
$BaCl_2$ and H_2SO_4....	1 : 400,000

A further consideration of the above figures makes it seem improbable that the quantities of the poisons mentioned are so uniformly distributed in the organism as is assumed in the calculation. We are rather led to the view that a localization or concentration takes place at those parts that are affected, in somewhat the same manner as a woolen thread can concentrate and make distinctly visible a very slight and uncertain color in a solution. And indeed it has been possible by intravital staining with proper dye-stuffs to furnish proof of such a localization within the organism. Thus, for example, methylene blue imparts a particularly intense color to the nerve endings, certain cells of the pancreas and a definite category of muscle fibers endowed with particular functions.[1] At the same time it has been possible by means of this same coloring-matter to establish differences in chemical characteristics of the cells which absorb it. It is taken up in part as a leuco base and in part is transformed into a compound which regenerates methylene blue only on treatment with hydrochloric acid.[2] The power of coloring gray nerve matter is possessed by only a small number of dyes, especially basic dyes. All dyes that contain a sulphonic acid group are in this respect entirely ineffective and of the acid dyes containing hydroxyl as the auxochrome group alizarine alone is effective.

Phenomena of this sort, at first noted only as interesting facts, were utilized later, particularly by Ehrlich, as a basic starting point for a comprehensive tracing out of physiological action. We must tarry for a moment while on this interesting point. The first question which naturally arises is how we can recognize a localization when we are dealing with substances other than those we have just discussed—that is, with substances whose presence cannot be plainly detected by the eye, as is the case with coloring matters. When we have under consideration the living being, then, of course the hypothesis that such localization is the cause of the general physiological effect, helps us out of our difficulty. By careful study of the physiological effects we can determine when the ingested foreign substance has become localized if we know the seat of the function that has been affected. Thus we may learn the organ upon which this function is dependent and so the brain centers and nerve fibers concerned in the effect. For all such information as this we are of course indebted to the present state of development of anatomy and physiology. Naturally we must determine by experiment in the individual case whether the influence is to be traced to the organ itself or to the brain center that controls it, or whether the nerve fiber that connects the two has been affected. Further observations can be made in the post mortem examination of the affected individual. Some substances leave at the seat of their localization distinct evidences in the form of histological changes; for example, the ecgonine derivatives in the parenchyma of the liver (Ehrlich) and curare in the nerve fibers (Cavallié). The localization of other substances can be detected directly by staining or by the addition of a proper reagent. Thus, for example, it is possible to trace the iron absorption from the intestines by the intestinal epithelial cells, the lymphatic glands, etc., by treating the organs under suitable conditions with ammonium sulphide or with potassium ferrocyanide. Thus, also it is possible to ascertain the distribution of aniline in the organism by means of 1-2-naphthoquinone-4-sulphonic acid.[1] The further development of physiological and histological anatomical methods will very probably bring to light many other possibilities in this field.

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[1] Ehrlich, Leyden-Festschrift, Vol. I.

[2] Herter, Z. physiol. Chem., 42, 493 (1904).

We may add that the localization of the toxines, immuno bodies, etc., which are so exceedingly sensitive in their reaction, can quite frequently be directly demonstrated by means of solution of the corresponding antibodies.

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[1] Ehrlich and Herter, Z. physiol. Chem., **41**, 379 (1904).

Now this selective power, which has already been determined for a great number of substances and which we can reasonably expect to exist for many others, may depend upon either physical or upon chemical causes.

Ehrlich compares the power of resorption possessed by individual organs for certain substances to the shaking-out process for alkaloids from their aqueous solution by means of organic solvents, such as ether, benzol, ligroin, etc. If we bear in mind that the liquids circulating in the body (blood and lymph) are essentially aqueous in character, but that the organs of vital importance, such as blood corpuscles, brain and nerves, are distinguished by a content of fatty or wax-like substances, such as lecithines and cholesterines, then many physiological effects suggest the comparison. Hans Meyer[1] as well as Overton[2] have shown that at least in the case of the neutral narcotics we have to do with more than a mere comparison, as here the degree of action increases in the same ratio as the quotient:

Solubility in fat : solubility in water.

There had previously been recognized relationships between the fat content of the brain and the degree of narcosis[3] that led von Bibra and Harless to the assumption that the essential feature of narcosis is the extraction of fat substances from the brain. This view has more recently been supported by the experiments of Reicher.[1] Further, Hermann has shown that all narcotics of the fatty series can dissolve red blood corpuscles, and has explained this phenomenon as an extraction of their fat-like substances. At the same time he calls attention to the coincidence of this process with the presumptive occurrence of narcosis. Reicher, on the other hand, had pointed out that the narcotic power of a substance is inveresly proportional to its solubility in water.

---

[1] Hans Meyer, Arch. exp. Path. Pharm., **42**, 109 (1899) and **46**, 337 (1901). Baum, ibid., **42**, 119 (1899).

[2] Studien über die Narkose, Jena, 1901.

[3] Kochmann, Biochem. Zentr., **4**, 689 (1906).

The theory of Overton and Hans Meyer may be summed up in the following theorems propounded by them:

(1) All primarily indifferent substances that are solvents for fat and fat-like bodies must act as narcotics upon living protoplasm cells if they can be absorbed by the cells.

(2) The action must appear first and strongest in those cells in whose composition these fat-like substances predominate and in which they are especially essential contributors to the cell-function—in the nerve cells, therefore, before all others.

(3) The relative power for action of such narcotics must be dependent on the one hand upon their mechanical affinity for fat-like substances and on the other hand their lack of affinity for the remaining cell substances—that is, principally water. So we can say their power depends upon the degree of their partition between water and the fat-like substances.

This theory is borne out and substantiated by the finding of similar relationships in other than the fatty series; but we cannot say that solubility in fat alone is the cause of narcosis. For such a conclusion as that would very apparently imply that the neutral fats should be counted among the most powerful of narcotics. So we must conclude that aside from these factors of solubility there must be taken into account some chemical factors of no less importance.

---

[1] Reicher, Z. klin. Med., **65**, 235 (1908).

Kochmann with perfect justice raises the objection that if the theory of Meyer is entirely valid all narcotics that act on the central system would of necessity act upon the peripheral nerves, at least temporarily paralyzing them, because they are very decidedly rich in lipoids, even if not to such an extent as is the brain. But, according to Gradenwitz,[1] this is not the case.

Now there are very definite observations that point to the presence of chemical action in narcosis.

The objection may very properly be made to the theory of von Bibra and Harless that the rapid return to the normal state contradicts it. This is Kochmann's argument.

Neverthless the fact which they have established remains—that is, that the quantity of fat capable of being extracted (from the brain during narcosis) is less than the quantity that can normally be extracted. Therefore, if this fat has not been removed from the cells, it must have undergone a change through the action of the narcotic. Moore and Roaf[2] have shown that chloroform and other anæsthetics combine with protoplasm to form unstable compounds, and they presume that the formation of such compounds is the cause of the intoxication. The possibility of the formation of such compounds by the union of substances supposedly incapable of chemical combination has been thoroughly discussed by Heymans and de Buck.[3]

---

[1] Gradenwitz, Dissertation, Breslau, 1898.

[2] Moore and Roaf, Proc. Roy. Soc., **73**, 494 (1904); and **77**, 86 (1906).

[3] Heymans and de Buck, Arch. intern. pharmacodyn., **1**, 1 (1894).

So Kochmann fairly propounds the question: does the solubility in the fat perhaps merely serve as a means to an end? It may be absolutely necessary only in order that the narcotic may enter the cell without being an etiological causative factor. In view of this discussion we must decide that the power to dissolve in fat is essential as the chief cause for the entry of the narcotic into certain organs. Therefore this factor within a given group of substances related in action will determine the degree of their activity.

A treatment similar to the one we have made concerning solubility may also be applied to osmotic pressure and to surface tension in order to explain physiological differences in action of various substances. Nothing could be more desirable than to subject to mathematical treatment the complicated situation which we have in the action of foreign substances in the organism. But as yet we should have to deal with too great a number of variables at one time, and until some of the relationships that are still almost unknown to us shall have been positively established, such a treatment can hardly be applied. A premature attempt of the sort, which frequently results in treating as negligible factors the clear deductions of physiological observations, can only lead to discredit of the mathematical method.

Loew[1] assumed a direct chemical union of the protoplasm with the so-called substituting poisons, supposing the labile amino and aldehyde groups of the protoplasm to be active in effecting such a union. In such a case then, the poisonous substances to be considered must have certain groups which are capable of reaction with these amino and aldehyde groups even in very dilute

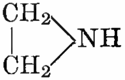
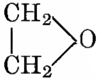
[1] Loew Ein natürliches System der Giftwirkungen, Stuttgart (1893).

solutions. Such an explanation seems to be, at least in some instances, quite plausible. For example, hydroxylamine and the hydrazines, which are well-known aldehyde reagents, are powerful poisons for vegetable and animal organisms, while the ketoximes, in which the reaction group is bound, are only in exceptional cases more poisonous than the related ketones. Moreover, aniline, which reacts with aldehyde with far greater difficulty than does phenylhydrazine, is also, as we should expect, far less poisonous. In the case of a few poisonous bodies having a tertiary nitrogen, a reduction with the formation of an imino group and consequently greater chemical activity increases their poisonous effects. In this connection may be mentioned the reduction of pyridine to piperidine. It is quite presumable also that in this category should be placed those bases whose power for action may be diminished by the entry of alkyl groups. This is particularly the case when an acid radicle is introduced into an amino group. In other cases, however, this hypothesis fails and is not supported by the facts. Erhlich will not admit this hypothesis at all for ingested foreign poisons, because in his very numerous experiments in this direction he was never able to establish that there had been a chemical union of such bodies. In fact, he found that the various poisons could, without exception, be again extracted from the tissues by means of neutral, chemically inactive solvents. Further, he opposes the Loew theory with the following arguments.

(1) The return from a condition of narcosis to the normal condition is rapid in the case of most of the substances under consideration.

(2) When dye-stuffs (such as fuchsine) which are capable of reacting with aldehyde to suffer a distinct

color change are used, there is no occurrence of such change.

Ehrlich, however, assumes a real chemical union in the case of toxines of high molecular weight and in the case of substances such as food-stuffs which are capable of assimilation, and in such cases he maintains that the specific haptophoric groups of the substance combine with the receptors or side chains of the protoplasm. For foreign substances, he concludes as a result of his investigations, that there is such a union only in the case of dimethylenimine  and for the structurally analogous dimethylene oxide  because these substances effect a lasting and peculiar change in the tissue.

Although we must acknowledge that the objections to the theory of Loew are in part justified, nevertheless, they themselves are not beyond criticism nor wholly free from fault. It is safe to presume that there are a number of substances that would show an action on the tissues similar to that of dimethylenimine. In fact, according to Ehrlich's investigations, cocaine and most of the other ecgonine derivatives cause a characteristic foamy degeneration of the liver cells, and a more delicate microscopic technique has shown that cocaine and stovaine, which acts similarly, develop in the localities of their action certain well-marked structural changes.[1] It will, therefore, without doubt, be necessary to widen the circle of exceptions to the Ehrlich law, and among these exceptions are most certainly to be included, according to Ehrlich's own beautiful researches, the compounds or combinations of trivalent arsenic in their behavior toward trypanosomes.[1]

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[1] Santesson, Skand. Arch. Physiol., 21, 35; Chem. Zentr., 1908, II, 145.

The most weighty of the reasons adduced by Ehrlich in support of his contention is the fact that the poisonous substances can be removed from the tissues by means of neutral solvents. But even supposing a chemical union, this phenomenon can be explained by the law of mass action by assuming that the various protoplasm compounds are easily dissociated in the solvents. This would at the same time explain the evanescence of the narcosis.

In fact, we find in Overton's work some results that indicate such a behavior. For example, if we place certain cells in a strychnine solution, there is formed within the cells a precipitate of strychnine tannate. This formation is proportionate to the concentration of the alkaloid in solution, and if this concentration is decreased by sufficiently diluting the solution, the precipitate will disappear. Accordingly, a chemical union of the poisons would seem quite probable if their removal from the tissues proceeded only according to laws other than those that hold in the case of ordinary mixtures of substances. And, in fact, this is supported by investigations of Straub[2] who found that certain effects of alkaloids are dependent upon a preliminary storage in the sensitive cells. He also found that inactive alkaloids are either destroyed or are not stored up in the cells. Straub proved such a storage effect in the case of veratrine, and he further showed that here the partition coefficients differ from those demanded by the diffusion law. Denarcotization is also effected by the blood and tissue fluids much more strongly than we should expect according to this law. Therefore, we must consider the fixation of the poison on the protoplasm and its removal as a reversible reaction which may be represented by the following equation:

---

[1] Ehrlich, Ber., **42**, 30 (1909).

[2] Straub, Pflüger's Arch., **98**, 233 (1903).

$$\text{Plasma} + \text{poison solution} \rightleftarrows \text{poison plasma} + \text{water}.$$

Other instances of chemical fixation have already been mentioned in the discussion of the Overton-Meyer theory.

However this conflict of opinions as to the mechanism of the action may be decided, this at least is certain: The production of an effect at any desired place in the organism necessitates such a chemical constitution of the ingested substances as to make possible their local fixation, whether it be of a chemical or of a physical nature. When there is such a structure of the material, this acts, we may say, as a grappling hook by means of which the effective groups can be attached or hooked on to the substance of the tissue.[1]

It is necessary, of course, to avoid the previous accumulation in the protoplasm of such groups as have the same or a similar selective tendency as the substance we desire to bring into action. Otherwise our efforts at directive medication would be fruitless. This discussion clearly emphasizes the great practical value of research upon the mode of action of the different substituting groups and upon the group characteristics which enable them to react upon or become attached to the different body organs. It is also apparent that the synthesis of medicinal preparations depends upon the scientific advance of such considerations.

[1] Ehrlich, Leyden-Festschrift.

A research of this sort is conducted in two different ways. At first it was naturally directed to substances that had been determined in an empirical manner to be physiologically active. These were of course natural substances, principally plant products. The first object was to isolate from the raw product whether drug or coal tar, those chemical components which constituted the active principles. This course has been pursued for many decades since the isolation of morphine from opium, and is still being pursued to-day. Such activities have been remarkable for the energy which has been spent in them and for the resulting successes. Coincident with such work, particularly in later years, has been the work of unraveling the chemical constitution of the active principles obtained. Then followed the attempt to determine what particular parts of the molecule, what special groups, were responsible for the specific physiological action. For example, it is extremely interesting and valuable from a chemical standpoint to have the total synthesis of an alkaloid. But it is far more important from the standpoint of practical medicine to be able to modify such a body so as to deprive it of undesirable or unpleasant effects while still retaining its essential physiological properties or to increase or strengthen the desired effect, or lastly, to combine this with other desired effects which are lacking in the original substance. These efforts must be carried still further in order to make ourselves independent of the original substances of nature, and to make in their stead artificial substances, similar, but constituted as simply as possible.

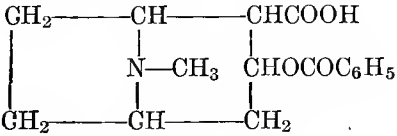
At the beginning of this work it was natural that it should be mainly directed toward the thoroughly known effects of substances traditionally offered us by nature.

But soon the investigators were ready to leave this path to explore physiological effects with which the older observers were necessarily quite unacquainted. How much there may be that is physiologically not only interesting, but indeed valuable in the almost countless numbers of compounds which the speculative investigation and experimentation of the chemists have given us since Wöhler's synthesis of urea! Enormous as these possibilities are, they must continue to multiply to far greater numbers in the future.

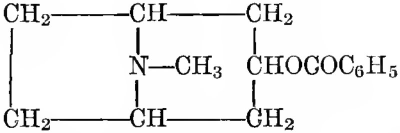
The second direction in which effort has turned for quite a period of time is the determination of the physiological behavior of many active chemical groups, some of them long known and some newly discovered. It is to be urgently desired from both a practical and a theoretical standpoint that this work will be conducted in a much more comprehensive and thorough way than hitherto. For, up to the present time, this work has been usually done by pharmacologists either directly employed or supported by chemical factories, and it has been carried out merely with a view to its practical exploitation. Such work has had no real scientific aim and purpose. The theoretical development of the subject demands more thorough methods of investigation. The pursuit of vaguely suggested and often undesired effects can be successfully carried on only by the cooperation of the chemist and the physiologist. Thus only will the theoretical views on the influence of constitution be placed upon a secure and safe foundation. And it is almost self-evident that such investigation will be followed by an immense amount of information of practical value, at least in a general understanding and conception of the subject. Such investigations are of sufficient importance for the welfare of mankind to warrant the foundation and support by state authorities of institutions properly equipped and independently endowed to carry on the work. The pharmacological university institutions which are carrying the burden of education with their few and underpaid professors are entirely inadequate to cope vigorously with this problem.

The greatest care and painstaking detail are of course paramount in importance in the development of this science. There must be the most thorough reliability in the work of the chemist in unraveling the structure of the compounds which he has prepared as well as in the work of the physiologist and physician in interpreting the symptoms which are provoked. The technique of the work is as yet in its developmental stage, and still leaves much to be desired. We may hope that in time many an obscure and hitherto inexplicable phenomenon will find its explanation.

Especially is the greatest care also demanded in judging and interpreting the results of experiments. For example, it happens occasionally that a faint suggestion of an effect in the initial substance is very considerably increased by the introduction of a new group. The almost self-evident inference is that this new group is in itself responsible for such an increment in the observed effect. But this conclusion may be quite erroneous, since the influence of the new group may essentially depend upon the fact that it neutralizes another effect which predominated in the initial substance, or that it, so to speak, paralyzes the action of a group that obstructed the prominence of the desired effect. Thus, for example, there is formed from the mildly anæsthetic benzoyl ecgonine,

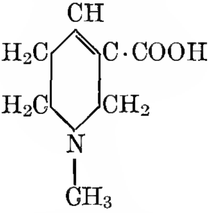


by alkylation the powerfully active cocaine; but benzoyltropine,

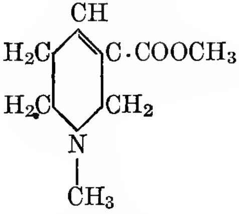


is also powerful in its anæsthetic effect. Therefore, we can conclude that the alkylation of the carboxyl group in benzoylecgonine does not impart the anæsthetic properties to the compound; but it does neutralize the inhibitory qualities of the carboxyl group. There is a similar relationship between arecoline II and arecaidine I:

I Arecaidine



II Arecoline



It must be clear that in such cases only the most painstaking consideration of analagous cases in the greatest possible variety can lead us to a correct interpretation of results.

Great care is likewise necessary in quantitative comparisons of effects. The mode of distribution must be carefully taken into account. For example, we must consider that differences in solubility may often account wholly or in part for deviations from the expected localization possibilities of a drug or poison. Add to this the fact that probably in the case of every substance ingested we must admit that a certain quantity is necessary before any effect will be noticeable. Comparisons of intensity of effect should be made only after passing this initial quantity. Especially is this consideration of importance in cases where the ingested substance is normally present in the organism. Under such conditions a certain adjustment of the normal organism has been already established for the material in question.

It is, of course, only in exceptional cases that we find monotropic substances. By this we mean substances that are limited in action to one organ, or still more correctly, to one element of one organ. New difficulties and new complications in judging the relative strength of effect arise from the differences in the points of attack or action of substances upon the complicated higher organisms. The attempt has been made in more recent times to avoid this difficulty as far as possible by making the experiments on the lowest life forms, such as the unicellular organisms of bacteria, paramæcia, yeast, sea urchin eggs, red blood corpuscles, etc. As one would expect, the results obtained in this manner are very well comparable among themselves. But it is clear that in order to reach conclusions which are applicable to the higher animal organisms from the results with these lowest forms, it would be necessary to make an enormous number of different experiments on the most divers cell kinds. For there have been observed the greatest differences imaginable in the effects of some groups upon warm- and upon cold-blooded animals. Not only that, but there have been found differences of behavior in the most nearly related species. For example, the extraordinary diminution of the poisonous effect of *p*-aminophenyl arsinic acid by acetylization while observed in the case of the mouse is only slight in the case of other animals. In the case of the morphine derivatives, the only experimental results that are comparable with the effects on the human organism are those obtained on the organism of the cat. We must mention here the quite valuable investigations that have been made on isolated organs retained in their state of normal functions by means of an artificial circulation of blood.

But there are sometimes individual differences even in the same animal kind. That such is the case even in the lower forms of life is shown by the occurrence of some trypanosome types that are immune to poisons through an established tolerance. In the higher forms of life and particularly in man, this phenomenon is very strongly pronounced and very varied. It is known under such names as idiosyncrasy, tolerance and immunity. Some substances have been observed to act differently under normal physiological conditions and under pathological conditions. Thus, quinine will reduce the temperature of a fever patient from 3° to 4°, while the temperature of a normal person is only slightly lowered. Salicylic acid is powerfully active in this direction in cases of acute articular rheumatism, while it is but slightly active in other febrile affections and is inactive upon the normal body.

Now, it will be quite evident that conditions are very complicated indeed when one wishes to act upon living organisms such as injurious parasites within another living being. Inner disinfection by chemical means in bacterial affections has remained, as is shown in the case of the phenols, a pious hope, a consummation devoutly to be wished for. It is quite true that the specific serum therapy will have to be referred for its ultimate reasons to chemical effects, although the elucidation of the chemical processes herein involved is still in its very infancy. But we already know that in some cases of serum therapy we have to deal with the concomitant action of lecithins and other lipoids, and perhaps soaps. The conditions seem to be more favorable, however, in the battle against animal parasites, where iodine, arsenic, and mercury compounds and certain dye-stuffs have been shown to be efficient in doses not injurious to man. In the case of dye-stuffs particularly there has been established a distinct relationship between constitution and effect upon the organism.

Some substances do not act as such for themselves, but only through secondary products, which are formed from them in the organism. The knowledge of such transformations forms an important field of our study, a field, however, which we can but casually touch upon in this treatise.

INORGANIC COMPOUNDS

In the action of inorganic substances we have to deal with other considerations besides the local effects such as are produced especially by free acids and alkalies. There is above all the effect of the water, and in the case of salts, since these are either used in solution or dissolved in the body, there are the various conditions dominant in solutions. The salts in part dissociate into their ions, and these, together with the undissociated salt, are the cause of osmotic pressure. According as the solution is hypotonic or hypertonic it will either cause a flooding of the tissues or will effect an abstraction of water from them. In the case of hypertonic solutions, we have to deal with salt action in its proper sense, which manifests itself preponderatingly in an increase of diuresis.[1] Further, the ions are the cause of specific effects. Blake[2] in his investigations, which extended over several decades, determined that these effects are due essentially to the electropositive components. By directly introducing the substances into the circulatory systems of living animals, he arrived at the following conclusions:

(1) The action depends only upon the kations, and has only very slight connections, if any, with the anions.

(2) In the same isomorphous group the activity bears a distinct relationship to the atomic weight, the in-

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[1] Sollmann, Am. J. Physiol., 9, 13, 454 (1907).

[2] Blake, Compt. rend., 1839; Proc. Roy. Soc., London, 1841; Am. J. Sci., 1874; Ber., 14, 394 (1881).

tensity of activity increasing with the atomic weight. The following groups are qualitatively equivalent:

(*a*) Li, Na, Rb, Tl, Cs, Ag, (K and NH_4 do not fall in this series);
(*b*) Mg, Fe, Mn, Co, Ni, Cu, Zn, Cd;
(*c*) Ca, Sr, Ba;
(*d*) Th, Pd, Pt, Os, Au.

Blake characterizes these group effects in detail as follows:

(*a*) Monovalent elements exert a powerful astringent or contracting action upon the capillaries of the lungs. They circulate through the nerve centers in greater concentration than through the lungs, and they exercise no appreciable effects upon the body capillaries.

(*b* and *c*) The salts of all divalent elements cause no contraction of the capillaries of the lungs. They are, however, detrimental to the heart action, and if administered in sufficient quantity inhibit it entirely. In smaller quantities the substances of the magnesium group (*b*) act directly upon the hæmogastric nerve, and presumably they act indirectly, by a reflex action, upon the intestine nerve (nervus splanchnicus). The members of the calcium group (*c*) act upon the spinal cord, causing spasmodic contractions of the voluntary muscles.

(*d*) The salts of the trivalent and tetravalent metals act principally upon the inhibitory as well as upon the vasomotor centers of the medulla oblongata. For the different valences of the same element there are characteristic differences in the compounds. In general, with increase in valence of the element there is an increase in the number of organs affected. Thus, ferrous compounds affect fewer organs than ferric, etc.

Blake later arranged the elements in isomorphous series, according to their atomic weights and the degree of their toxicity. The following is his table, the atomic weights being taken by him from the international table for 1908:

Group.	Element.	Atomic weight.	Lethal dose for 1 kgm. of animal body.
(*a*)	Lithium	7.03	1.2
	Rubidium	85.5	0.12
	Caesium	132.9	0.12
	Silver	107.93	0.028
	Gold	197.2	0.003
(*b*)	Magnesium	24.36	0.97
	Iron (II)	55.9	0.32
	Nickel	58.7	0.18
	Cobalt	59.0	0.17
	Copper	63.6	0.17
	Zinc [1]	65.4	0.18
	Cadmium [2]	112.4	0.085
(*c*)	Calcium	40.1	0.50
	Strontium	87.6	0.38
	Barium	137.4	0.08
(*d*)	Aluminum	27.1	0.007
	Iron (III)	55.9	0.004
	Yttrium	89	0.004
	Cerium (III)	140.25	0.005
	Cerium (IV)	140.25	0.062
	Thorium	232.5	0.034
	Lanthanum	138.9	0.025
	Didimium	142	0.017
	Palladium	106.5	0.008
	Platinum	194.8	0.027

We may add that uranium with the high atomic weight of 238.5 is exceedingly poisonous.—Kobert, Arbeiten, **5**, 1 (1890).

[1] Gallium with an atomic weight of 70 is according to Rabuteau slightly more active than zinc.—Rabuteau, Compt. rend. soc. biol., **35**, 310 (1883).

[2] Compare Athanasiu and Langlois, Ibid. **47**, 391, 496 (1895).

As before mentioned, potassium occupies, according to Blake's investigation, an exceptional position, which he, as in the case of nitrogen, connected with deviations observed in the behavior of the spectrum. Sodium, on the other hand, does not fit into the series in a quantitative way. This exception on the part of sodium may be explained by the odd and peculiar position of that element as a special sub-group of the alkali metals in the Mendelejeff system. There is also another point of view, which we shall reach later, which will enable us to understand this peculiarity. Potassium and ammonium share with the other monovalent kations the property of acting upon the capillaries of the lungs. At the same time, they possess like the calcium group, with which they are both isomorphous, the property of contracting the voluntary muscles. Potassium is at the same time a powerful cardiac poison.[1] This same property is also observed to a certain degree to be possessed by cæsium and rubidium. In this case then, the intensity of action increases with diminishing atomic weight. Therefore, contrary to the original formulation of Blake, but in accordance with the demands of the periodic system, potassium shows properties in common with the other alkali metals (excepting sodium). Furthermore, quite in accord with these facts, the " typical " element lithium has only the faintest suggestion of the cardiac effect.[2]

Binet has carried out a more exhaustive investigation of the alkalies and alkaline earths[3] According to his experiments, both groups in common cause in the central nervous system a diminution of susceptibility for excitation and they also cause a disturbance in the power of contraction of the muscles. Preceding the latter effect there are to be observed disturbances in respiration and in heart action. In the case of warm-blooded animals, these may cause death before the first general effects mentioned above become appreciable. There are found sometimes also (particularly in the case of barium and lithium) [1] disturbances in the alimentary canal. Besides these differences we observe strikingly characteristic and different effects for the chemical groups of the metals. Thus, the alkalies cause stoppage of the heart in diastole besides a motor inactivity through a general relaxation of the muscles. The alkaline earths, on the other hand, stop the heart in systole. Magnesium resembles the alkali group in that it stops the heart in diastole, but it is distinguished from that group in causing an early paralysis of the peripheral nervous system. In the case of mammals, barium is the most poisonous element of the group for heart action and respiration. It is further characterized by contraction effects. Calcium acts predominantly upon the central nervous system, producing a state of rigidity with retention of reflex excitability and sensibility.

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[1] Astolfoni, Arch. intern. Pharmacodyn., **11**, 381 (1903).

[2] Botkin, Zentr. med. Wissensch., 1885, No. 48.

[3] Binet, Compt. rend., **115**, 251 (1892).

Lusanna [2] investigated the action of metallic chlorides upon respiration and contractility in the faradic excitation of the frog muscle, using solutions isotonic with a 7 per cent sodium chloride solution, and arrived at the following results:

	Respiration depressed.	Respiration not affected.	Respiration increased.
Contractility destroyed.....	Ca, Hg, Cu Ni, Co	K	NH_4, Ba
Contractility not affected...	Li, Mg	Na, Sr	

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[1] Good, Am. J. med. sci., Feb., 1903.

[2] Bull. soc. méd., 1907, No. 4.

According to Hébert[1] thorium, cerium, lanthanum, zirconium, aluminum, and magnesium are posionous for fish, plants, aspergillus niger, yeasts and soluble ferments. The toxicity increases from magnesium (atomic weight 24.36) to lanthanum (138.9), to cerium (140.25), to chromium (52.1), to aluminum (27.1), to thorium (232.5). There can be seen no relation whatever in this case between toxicity and atomic weight.

There have rather recently been discovered in the case of magnesium, some very peculiar effects which remind one of certain alkaloids. According to Meltzer[2] solutions of magnesium salts injected either subcutaneously, intravenously or directly into the canal of the spinal cord cause anæsthesia and retard respiration. Upon administering large amounts, the tonus of the vasomotor center is impaired and somewhat before this the tonus of the pneumogastric center is so affected, and there is observed a deep general stupefaction with relaxation of all the muscles. Of practical importance is the statement of Meltzer that a deep general narcosis can be obtained with quantities that do not influence heart action, blood pressure, or respiration. According to different authors,[3] we have to deal with a curare-like action on the motor nerve ends while the sensory nerves are said to be not at all affected. On the contrary, Delhaye,[4] found that the diminution of excitability is manifested more quickly and more intensely in the sensory than in the motor nerve system—that in the former it is central and that it is curare-like only in regard to the motor endplates. According to him the injurious effect of this treatment upon respiration and upon the kidneys (resulting in a diminution of the quantity of urine and the appearance of albumin and cylinders in the urine), must preclude its therapeutic use.

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[1] Hébert, J. physiol. path. gén., **9**, 217 (1907).

[2] Meltzer, Berl. klin. Wochenschr., **43**, No. 3 (1906); Meltzer and Auer, Am. J. physiol., **21**, 449 (1908).

[3] Wiki, Soc. biol., **60**, 1008 (1906); Bardier, Soc. biol., **62**, 843 (1907).

[4] Delhaye, Bull. soc. roy. sci. méd. nat., Brussels, 1908, 72.

The fundamental characteristic effect common to manganese, iron, nickel, and cobalt, according to Wohlwill,[1] is the production of capillary hyperæmia of the stomach intestinal tract, and a consequent change in blood pressure. This together with a direct action on the central nervous system is probably responsible for the nervous symptoms exhibited under treatment with these substances. The manner in which these metals act is very similar to the action of arsenic. But they differ from arsenic in that they are not resorbed by the stomach and intestinal tract.[2]

It is already apparent from what has been said, that the Blake laws are not universally valid. This is particularly noticeable in the case of the action of anions, an action which is practically denied by Blake. He himself, however, made a note of the difference in behavior of sodium orthophosphate and the pyrophosphate which like the metaphosphate is poisonous. He sought to explain this difference by attributing it to greater hydrolytic dissociation, resulting in the liberation of a larger amount of free alkali. But this explanation will not hold. Differences similar to those found in the phosphoric acids also occur in the case of the vanadic acids.

Blake's negative results never referred to the halogens and cyanogen, although their specific effects are incontestable. According to Bouchardat and Cooper,[3] the general tendency with the halogens is a diminution of effect with increase of atomic weight. But the relationship is different in the case of the sodium salts. For here the fluoride is most poisonous. Then follow in order the iodide, bromide and chloride. Their comparative toxicity may be judged by the following toxic doses: fluoride, .02 gm.; iodide, 8 gms.; bromide, 10 gms.; chloride, 40 gms.

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[1] Wohlwill, Arch. exp. Path. Pharm., **56**, 404 (1907).

[2] Shumoff-Sieber, Biochem. Ztr., **2**, 190 (1906).

[3] Fränkel, Arzneimittelsynthese, 2d Ed., p. 5.

There is an essential difference in action between the halogen salts and the sulphates in that the former are easily resorbed, while the latter are resorbed only with decided difficulty with the result that the sulphates exhibit a specific saline action in the form of a purgative effect.

According to Pauli[1] all ions act upon albuminous substances, but there is an antagonism or opposition between the two kinds. The kations precipitate such substances, while the anions exhibit a counter effect. The purgative action is related to this capacity for precipitating albumin. Thus, the purgative effect increases from the slightly astringent and laxative alkali salts to the heavy metal salts, which cause caustic and gastroenteritic effects.[2] Among the anions themselves also, the counterprecipitation and accordingly the antipurgative tendency varies, the halogens being most active in this respect. And of the halogens iodine is most effective, although it is exceeded by sulphocyanide.

For salts of the alkaline earths the anions can be arranged in the order of the counter precipitation effect as follows: $SCN > I > Br > NO_3 > Cl > C_2H_3O_2$. For salts of the alkalies the arrangement is reversed, viz.: $C_2H_3O_2 > Cl > NO_3 > Br > I > SCN$. The kations may be arranged in the order of their precipitating power as follows: $Mg > NH_4 > K > Na$.[1]

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[1] Pauli, Münch. med. Wochschr., **50**, No. 4 (1903).

[2] Hofmeister, Arch. exp. Path. Pharm., **24**, 247 (1888).

But we must remark here that the total specific action upon the organism does not necessarily accord with the ion effect. This is strikingly illustrated by the action of alkaline earth ions in regard to the SCN action. The alkaline earths are not themselves precipitants. Nor are the sulphocyanides of the alkalies. Yet the two acting together will cause precipitation of proteids. In living animals that have been moderately dosed with sulphocyanides a subsequent dosage of barium causes an acute sulphocyanide poisoning, while strontium causes a hardly perceptible increase in the sulphocyanide action and calcium has no effect at all.[2]

In some other poison effects polyvalent kations can have an action antagonistic to that of the monovalent kations.

A certain concentration of sodium ions is necessary for the contractive action of frog muscles,[3] the Medusa Gonionemus,[4] and fibers or strips of the heart muscle of Chrysemis Marginata.[5] But if the sodium ions (or in their place lithium, rubidium, or calcium ions) alone are present, then they have a poisonous effect. If frogs' muscles are suspended in a pure 7 per cent solution of sodium chloride, they attain in about an hour a state of rhythmic spasms or convulsions that continues for twenty-four hours or longer.[6] Teleostier Fundulus and its impregnated eggs die quickly in a pure sodium chloride solution on account of the osmotic pressure of the sea water.[1] Gonionemus likewise stands a diminution of osmotic pressure better than a pure NaCl solution of normal pressure. This poisonous action of the sodium ions can be overcome by the addition of comparatively small amounts of trivalent kations. In the case of Fundulus and Gonionemus the poisonous effects are wholly destroyed by Ca, Ba, Sr, Mg, Pb, Co, $\overset{\text{II}}{\text{Fe}}$, Zn, $\overset{\text{II}}{\text{Mn}}$, Cr, Al, while they are in part removed by $\overset{\text{II}}{\text{U}}$ and $\overset{\text{II}}{\text{Th}}$. There is no such action at all by Hg, Cu, Cd, Ni, and $\overset{\text{III}}{\text{Fe}}$.[2] In the case of the frog muscles, the rhythmical convulsions or spasms are not stopped by Ba, Zn, Cd, and Pb, but they are stopped by K, notwithstanding the fact that it is monovalent.[3] And further, in the case of Fundulus and Gonionemus, the presence of K ions is necessary, besides that of the divalent ion for a complete restitution of the normal function. The reason for this necessity of a definite equilibrium of ions must probably be found in the action of the ions upon those colloids which are necessary for life.[4]

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[1] Pauli, Hofmeister's Beitr., 5, 27 (1904).

[2] Pauli and Fröhlich, Wien Akad. Ber., **115**, III, Abt., June, 1906.

[3] Overton, Pflüger's Arch., **92**, 115, 346 (1902).

[4] Loeb, Am. J. Physiol., **3**, 383 (1900).

[5] Lingle, ibid., 4, 265 (1900).

[6] Loeb, Festschr. für Fick (Beitr. z. Physiol.), p. 101 (1899).

Herbst[5] makes the observation that for the development of the eggs of Fundulus Mg ions are necessary as well as Na, K and Ca. Furthermore, he finds that the anions are not negligible, since chlorine, sulphuric acid, and carbonic acid ions are also necessary. To a limited degree, however, substitution of these ions by chemically related ones may be made. Thus, for example, S_2O_3 may to some extent be used to replace SO_4, Br to replace Cl, and Rb or Cs for K. Moreover, in some processes a certain excess of hydroxyl ions is necessary.

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[1] Loeb, Am. J. Physiol., **3**, 327 (1900); Pflüger's Arch., **80**, 229 (1900).

[2] Ibid., Am. J. Physiol., **6**, 411; Pflüger's Arch., 88, 68 and 93, 246 (1902).

[3] Ibid., Pflüger's Arch., **91**, 248 (1902).

[4] Hoeber, Biochem. Zentr., **1**, 497 (1903); Hoeber and Gordon, Hofmeister's Beitr., **5**, 432 (1904).

[5] Herbst, Arch. f. Entwickl. Mechanik, **17**, 306 (1904).

The hæmolytic action of human blood serum is unaffected by the addition of sodium chloride, potassium chloride, or lithium chloride, but it is destroyed by salts of the alkaline earths and also by an N/8 concentration of potassium sulphate.[1]

Mathews[2] emphasizes the importance of both ions, but interprets the results as a consequence of the different solution pressures and not of the different valences. According to his theory the poisonous effect of any given salt is inversely proportional to the sum of the solution pressures of the ions.

In interpreting the results of such investigations we must always consider that the poisonous effect of some salts may be prevented by a certain saturation of the cells with other and harmless salts. Thus, according to Lesne and Richet fils,[3] sodium chloride administered either simultaneously or previously protects the organism to a very considerable degree from the injurious effects of potassium iodide, ammonium chloride, and even of some salts of alkaloids. But this does not hold true for all salts, and in many instances no appreciable results could be found in this direction.[4]

We must also bear in mind that a tolerance already established in the organism which is being used for experimentation on the effects of various inorganic salts, plays a very important part in the results obtained. To this fact, perhaps, may be attributed the exceptional position of sodium in the series, for this element constitutes the principal inorganic component of the fluids (or humors) of the body. In this connection we may also note, that, as we should expect, herbivora can stand potassium salts far better than can carnivora. In the case of calcium, the lower the stage of development of the animal kind, the greater is the tolerance toward this element. Also it is found that tolerance for calcium is more easily established in youthful individuals than in fully developed ones. For all substances which naturally occur in the organism there may be assumed a certain initial value or concentration which must be passed before the effects are really comparable or measurable.

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[1] Hektoen, Zentr. Bakteriol., **35**, 357 (1904).

[2] Mathews, Am. J. Physiol., **10**, No. 6 (1904); compare Pond, ibid., **19**, 258 (1907).

[3] Lesne and Richet fils, Arch. intern. pharmacodyn., **12**, 237 (1903).

[4] Lesne, Richet fils and Noé, Soc. biol., **57**, 99, 238 (1904).

Quite in agreement with the assumption of ionic effect or action in these physiological studies is the great importance of the degree of dissociation which is very decidedly pointed out by the investigations of Dreser[1] and of Krönig and Paul[2] upon the bactericidal action of mercury salts.

From all this discussion it is self-evident that the action of the individual elements is very largely dependent upon the form of combination in which they act. The powerfully toxic effect of free phosphorus disappears at once when the substance is combined with oxygen, as even phosphorus suboxide is entirely lacking in toxic effect.[3] Arsenic is most toxic in its hydro-

[1] Dreser, Arch. exp. Path. Pharm., **32**, 456 (1893).

[2] Krönig and Paul, Zeitschr. physik. Chem., **21**, 414 (1896).

[3] Kobert, Therap. Gegenw., **5**, 59 (1903).

gen compounds and oxygen compounds, the trioxide having, of course, a particularly intense effect. The phosphonium and arsonium compounds have essentially the curare-like action of the organic quarternary ammonium salts. Finally, the compounds of the cacodyl type produce a characteristic arsenic effect proportional to the ease with which the organism can oxidize them to arsenic trioxide.[1]

The complex ions containing cyanogen with iron have an action not at all similar to their action as more simple ions. This point is clearly shown by the ferrocyanides, ferricyanides, and sulphocyanides. Furthermore, the different action of a single element with different valences may find its explanation in the difference of the corresponding ions.

Above all, although the ionistic conception has been sufficiently justified by other experiences, we must mention the difference in behavior ordinarily to be looked for when an element is bound up in organic non-electrolytes. The specific action of an element in such a condition can only be expected after its transition into the ionic state, and, therefore, it must generally come into play in a slow, mild, and continuous manner.

An example of such an effect has already been mentioned in the discussion of the cacodyl compounds.

The same explanation seems to hold in the case of compounds which have been recently accepted and much used of the type of *p*-aminophenyl arsinic acid. This substance is found in trade under the name of Atoxyl, and was formerly erroneously supposed to be meta-arsenous acid anilide.

While we are discussing the organic arsenic compounds it may not be out of place to devote some space to a consideration of a little of their history, and the path which has led to that most recent compound which has caused tremendous excitement even outside the scientific world—salvarsan.

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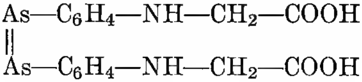
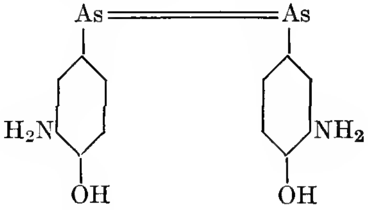
[1] Kobert, l.c.; Martinet, Bull. gén. Therap., **155**, 70 (1908).

As early as 1837 Bunsen observed that cacodylic acid seemed to be less toxic (for frogs) than inorganic arsenic compounds. But Lebahn showed in 1869 and H. Schulz in 1879 that cacodylic acid, dimethyl arsinic acid $(CH_3)_2AsOOH$ and also diphenyl arsinic acid are deadly poisons for warm-blooded animals, although slower in action than the inorganic arsenic compounds. Hefter, Kobert, and others arrived at the conclusion that such compounds act in proportion to their mineralization in the organism. There were various such compounds prepared and introduced for use; but the one which served as the starting-point for Ehrlich's investigations is the afore-mentioned Atoxyl. It was soon observed that the various compounds prepared did not act entirely as if their effect depended upon mineralization alone. In fact, they were observed to have specific effects against infectious diseases. This was first observed in the case of trypanosome diseases. Thereupon arsenic returned to the first application which it had as a popular remedy against recurrent fevers or malaria. Its usefulness against sleeping-sickness and other trypanosome diseases was determined in the French colonies by Laveran and Mesnil. Thomas, and later Robert Koch used atoxyl for combating the sleeping-sickness. A serious hindrance to its usefulness, however, was the pronounced side-effects and the slowness and uncertainty of the cure. It was then to be hoped that the effect upon the parasites might be increased and the effect upon the host decreased. The necessary changes in the constitution of atoxyl were made clear when Ehrlich and Bertheim discovered that the constitution ascribed to atoxyl was incorrect and that it is the mono-sodium salt of the long-known *p*-aminophenyl arsinic acid, $NH_2C_6H_4AsO_3H_2$, which is designated arsanilic acid. The first step in the variation of amino compounds is usually to introduce acid radicles. The introduction of acetyl gave a preparation called arsacetine, the sodium salt of acetyl arsanilic acid. This was effective and little toxic for some animals, particularly mice; but was not suitable for use upon man. A better compound was found when the acetyl radicle was attached to the amino group by means of the methyl instead of carboxyl. This gave arsanilacetic acid, $AsO_3H_2C_6H_4—NHCH_2COOH$. It was then found that trypanosomes in vitro were not killed by this compound, but by its reduction products, and that probably, as in the organic compounds of pentavalent arsenic, the real effect is due to a reduction in the organism to trivalent arsenic. Among such trivalent arsenic compounds which were found to be powerful against protozoa, but only slightly toxic for the higher organisms are the derivatives of amino-phenyl-arsen-oxide, $NH_2—C_6H_4—AsO$, and derivatives of diamino arsenobenzol, $NH_2—C_6H_4—As=As—C_6H_4—NH_2$, particularly arsenophenyl glycine,



$$\begin{array}{l}\mathrm{As—C_6H_4—NH—CH_2—COOH}\\ \| \\ \mathrm{As—C_6H_4—NH—CH_2—COOH}\end{array}$$

The next step that was taken was a further introduction of substituents in the benzol ring. It was found that ortho substitution of most groups impaired the effect; but halogen increased it. About the next advance was to try some of the trypanocides upon spirillæ diseases. Atoxyl was tried upon cases of syphilis. Its close derivatives were also tried, but in general the side effects are too great, compared with the advantageous action. The benzol sulpho derivative of atoxyl, however (which is called Hectine), and the mercury salt of arsanilic acid are said by some to be effective. It was next found that a powerful spirillocide was obtained by replacing with hydroxyl the amino group of di-para-aminoarsenobenzol. This gives para-arsenophenol. Then the most effective substance was found by introducing amino groups in the ortho position to the hydroxyls in arsenophenol. This gives dioxy-di-amino-arsenobenzol, whose hydrochloride is Salvarsan.



This compound is prepared by the nitration and subsequent reduction of para-oxy-phenyl arsinic acid, which is formed directly from phenol and arsenic acid. It was hoped and at first supposed that in this substance we had an agent which at one fell stroke could kill all the protozoa in the organism, and thus avoid the possibility of some of them becoming immune. But results have seemed to show that in some cases either some spirochetæ are relatively immune to the arsenic from the start or they are protected from its action by their location. Doubtless there are many cases that are promptly and permanently cured by salvarsan, as there are also many that are curable by mercury. In other cases, perhaps it is necessary to adopt a method previously indicated by Ehrlich—namely, that of combination therapy.

The disadvantages, which occasionally accompany the use of salvarsan are attributed by Ehrlich to its instability toward atmospheric oxygen. Neosalvarsan is the result of an attempt to avoid this deterioration due to the attack of oxygen. Salvarsan was combined with sodium methanal sulphoxalate. This compound dissolves readily in water with a neutral reaction to litmus, seems to be less toxic and more easily tolerated than salvarsan, and produces less injurious side effects.

In cases where the element itself in non-ionized form is active, as for example in the case of iodine, it seems that the effect is dependent upon a dissociation or breaking down into elementary form, which is somewhat similar to ionization.

But sometimes it seems to be just certain organic compounds of inorganic elements that exercise a peculiar and specific effect. In such cases, of course, for the attainment of this particular effect, the use of such compounds is from the beginning clearly indicated and to be expected. For example, such is pre-eminently the case for many iodine compounds. After a substance containing iodine had been extracted from the thyroid gland and had been recognized as its active constituent then iodothyrine, iodogorgonic acid, etc., obtained from this secretion were used to obtain the specific effects desired.

The advantages of the halogenized fats (Iodipine, Bromipine), and of the salts of the halogenized fatty acids (Sajodine, Sabromine) may be due essentially to their milder and long continued action on account of the necessity for a preliminary ionization. There is, however, the possibility that their advantage may be dependent upon a condition more favorable to resorption and assimilation. Such favorable conditions for assimilation have also been assumed to hold for organic iron compounds and also in various compounds through which phosphorus is introduced into the organism. Through such an assumption a special importance or efficiency has been claimed for the lecithins, glycerophosphoric acids, and particularly for Phytin, which is a double calcium and magnesium salt of anhydro-oxymethylene-diphosphoric acid. Whether or not all these assumptions will hold must be considered to be still an open question.

It is undoubtedly possible to cause the metals to penetrate further into the tissues if they are in combination in organic molecules than if they were in the form of electrolytes, because of the precipitating effect that such electrolytes have upon albuminoids. Thus, they may be employed to obtain results in otherwise unreachable places.[1] The importance of many compounds of this class depends upon this property or ability for penetrating the tissues in an unprecipitated condition. In this connection may be mentioned as an example the wide use of certain organic silver compounds such as Argyrol.

A special place in the science of medication is occupied by colloidal solutions of the metals. Since all influence of the anions is eliminated in such a case we may perhaps expect a particularly clear and undisturbed effect of the kations. It cannot yet be decided whether it is upon this fact that the professed great efficacy of these solutions in infectious diseases depends, or whether there is at the same time a catalytic effect.

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[1] Compare Pauli, Wien. klin. Wochschr., **17**, 558 (1906).

At all events it is quite certain that all varieties of metal colloids are not equivalent. Luzzatto[1] has made tentative experiments upon the influence of various colloids upon the resorption of medicinal substances.

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[1] Luzzatto, Arch. fisiol., 1905, II, 10.

ORGANIC COMPOUNDS

Aliphatic Series

According to Lauder Brunton and Cash, hydrocarbons act quite generally upon the nerve centers. In the aromatic series this action is principally confined to the motor centers, while in the aliphatic series it affects essentially the sensory centers. In the case of the aliphatic series there is a very pronounced narcotic and anæsthetic effect, whether the application is subcutaneous or by inhalation. According to a law propounded by Richardson[1] this effect increases (in the paraffine series) with the increase in carbon content of the molecule. Coincident with this narcotic effect, and in marked contradistinction to that caused by substances of the morphine group, there is observed a reduction of the reflex excitability.

Naturally the increase in effect of the members of the series with increase of carbon content finds its limit in the physical properties of the substances. The high boiling paraffines of high molecular weight are practically without any action on the organism. This is easily understood, since substances of the paraffine series are hardly capable of resorption and consequently their entry into the organs is possible only by evaporation, and is therefore dependent upon their vapor tension.

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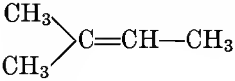
[1] Richardson, Med. Times and Gaz., 1871.

For a given carbon content unsaturated hydrocarbons act more powerfully than saturated hydrocarbons. Thus, for example, ethylene is much more active than ethane. In this connection we must observe that the double bonds in a cyclic system have less effect upon the intensity of action than do the double bonds in an open chain.

For example, let us consider the three hydrocarbons,

Pentane, $CH_3—CH_2—CH_2—CH_2—CH_3$

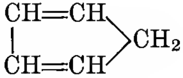
Pental,



$$\begin{matrix} CH_3\diagdown \\ \quad C{=}CH—CH_3 \\ CH_3\diagup \end{matrix}$$

and,

Cyclopentadine



Of the three we find pental to be most active, cyclopentadine second, and pentane least active.

Pental is perhaps the only body of this series which has found practical application. And we may remark that it exhibits a grouping which has also demonstrated its efficiency in other series. This grouping is an arrangement of alkyl groups about a center. As we shall soon note, the ethyl group is in general considerably more powerful in its effect than the methyl group. Now then, we should expect to be able to increase the activity of this body considerably by replacing the methyl by ethyl groups and also still further by the replacement of hydrogens by alkyl radicles.

In its fundamental character the narcotic action of the monobasic alcohols and their ethers, neutral esters, ketones, aldehydes and halogen derivatives is the same as for the hydrocarbons themselves. But the intensity of this action varies widely and is quite decidedly determined by the nature of the compound and the substituting group or element.

The halogen derivatives, and particularly the chlorine derivatives, show a very considerably greater hypnotic action than do the hydrocarbons. This increase in power depends, in the first place, upon the halogen content and is proportional to it. Thus, methane has a barely perceptible narcotic action. Monochlormethane is weakly narcotic, dichlormethane is still more powerful, and chloroform and carbon tetrachloride, as is well known, are both very powerfully active. Other effects besides the narcotic action also increase with increasing halogen content.

A depression of the heart and vascular activity is hardly noticeable in the case of the hydrocarbon. But it is plainly apparent with the halogen derivatives and is proportional to the halogen content. Thus, Zoepffel [1] found that the pulsations of a frog's heart were stopped after the administration of chloroform in only one-fourth the molecular concentration that was necessary for the same effect with dichlormethane.

Dichlormethane and carbon tetrachloride do not fall perfectly into the series because they produce powerful side-effects, manifested by convulsive spasms of such violence that the narcotic action is forced into a position of secondary importance. This special action, also, bears a definite relation to constitutional differences in composition. For, if we conceive of the halogen derivatives of the hydrocarbons as being the halogen acid esters of the corresponding hydroxyl bodies, then, as Brissemoret [2] showed, we can find a concordance between the actions of the hydroxyl compounds, as well as their alkyl ethers. Thus, formaldehyde and its acetals correspond to dichlormethane, while we have carbonic acid and its esters corresponding to carbon tetrachloride. Upon examining the other two classes of compounds, we find that methyl alcohol and methyl ether corresponding to monochlormethane, and ortho formic acid and its esters corresponding to chloroform, are, without exception, real anæsthetics or hypnotics.

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[1] Zoepffel, Arch. exp. Path. Pharm., **49**, 89 (1903).

[2] Brissemoret, Bull. gén. Therap., **153**, 657 (1907).

In the ethane series there are additional differences to be noticed, and these may be referred to the distribution of the chlorine atoms between the two carbon atoms. Thus, ethylene chloride and ethylidene chloride, although they both have the empirical formula $C_2H_4Cl_2$, show certain marked differences in narcotic effect and also in side effects.

The bromine derivatives show actions quite similar to those of the chlorine derivatives. Ethyl bromide has found application as an inhalation anæsthetic, and, although bromoform is not sufficiently volatile for this purpose, it has nevertheless been used for mitigating the paroxysms of whooping cough.

According to Binz,[1] iodoform taken internally acts as a narcotic and hypnotic. Mulzer,[2] however, denies that this is the case for all animal organisms. Such an action was observed by him for dogs, but not for rabbits. But there comes strongly into play in the iodine-substituted compounds another very important effect, and that is their antiseptic action. This has been generally attributed to the demonstrable liberation of iodine from the compound in the organism.[3]

With the substitution of hydroxyl for a hydrogen in the hydrocarbons the conditions become exceedingly interesting. With a single substitution we have, of course, instead of the hydrocarbon a monatomic alcohol. This increases the hypnotic action of the compound sufficiently so that these alcohols are practically useful hypnotics. In accordance with the Richardson law, we find the action to increase with the length of the straight carbon chain. So the longer the CH chain is, the greater will be the increase in hypnotic effect when the monatomic alcohol is formed. Furthermore, the secondary alcohols show a greater hypnotic effect than the primary alcohols, and the tertiary alcohols exhibit a still more powerful action. In these latter, particularly even more than in the secondary and primary alcohols, there is to be observed a specific influence of the ethyl group. For example, it requires the administration of as much as 4 gms. of trimethyl carbinol to induce sleep, while even 2 gms. of ethyl-dimethyl carbinol will induce a sleep lasting from eight to nine hours. And the administration of only 1 gm. of tri-ethyl carbinol induces ten to twelve hours of sleep.[1] But the practical application of this latter substance for its hypnotic effect is precluded, because of the side-effects consisting of difficulty in breathing when doses as large as 1 gm. are used and a powerful excitation for lesser doses. Thus, for practical purposes, the ethyl-dimethyl carbinol is the only one of these substances available for inducing sleep.

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[1] Binz, Berl. klin. Wochschr., **32**, No. 7 (1885).

[2] Mulzer, Z. exp. Path. Ther., **1**, 446 (1905).

[3] cf. Schürhoff, Arch. intern. pharmacodyn., **14**, 427 (1905).

This rather specific influence of the ethyl group which we shall later notice repeatedly seems to depend upon the fact that it has a special relationship to the nervous system. This has indeed been shown to be the case by color experiments of Ehrlich and Michaelis.[2]

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[1] Schneegans and v. Mering, Therap. Monatsh., 1892, 331.

[2] Leyden-Festschrift.

They showed that nerves were colored by dyes containing diethylamino groups, while they were not so affected by the corresponding methyl compounds. We must remark here, however, that this peculiarity of the ethyl group holds only in comparisons with the methyl group. Propyl groups we shall find equivalent to, or even stronger than ethyl groups in a given series. But we also find that the alkyl compounds of higher molecular weight are excluded from practical application—not because their narcotic effect is too weak, but because their undesirable secondary effect is too strong. Thus, it appears from an investigation by Räther[1] that we have the following relative toxic values as measured by the paralysis of conductivity for centripetal stimulus in a frog.

Point of stimulation.	CH_4O	C_2H_6O	C_3H_8O	$C_4H_{10}O$	$C_5H_{12}O$
Ischiadicus.......	1	3	18	36	120
Cornea...........	1	3	30	90	225
Foot.............	1	2	5	20	50

There is likewise found a regular increase in action from methyl to ethyl to propyl alcohols in their action upon ciliated tissue and motor nerve fibers[2] on the development of moulds[3] and of sea urchin eggs.[4]

In regard to that part of the influence which is due to the physical properties of the substance, we must refer to the general part of this work.

We have already noted that the substitution of hydrogen by halogen in the hydrocarbons increased the narcotic power of the compound. The same condition holds in the case of alcohols.

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[1] Inaugural-Dissertation Tübingen, 1905.

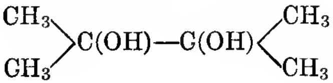
[2] Breyer, Pflüger's Arch., **99**, 481 (1903).

[3] Iwanhoff, Zentr. Bakteriol. (II), **13**, 139 (1904).

[4] Führer, Arch. exp. Path. Pharm., **59**, 1 (1908).

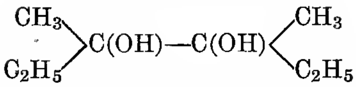
As a practical result of this knowledge we find a product put upon the market by the Elberfeld Farbenfabriken under the name of Isopral. This is trichlorisopropyl alcohol.

When several hydrogen atoms of the hydrocarbon are substituted by hydroxyl groups we must distinguish two different sorts of results. In the first place, if the substitution takes place on the same carbon atom, then the narcotic effect is either maintained or strengthened. The aldehydes and ketones (if we disregard their other properties) are decided narcotics. The same thing is true, as we have already mentioned, for ortho formic acid, acetic acid and their esters. But if the substitution takes place on different carbon atoms the result is different. For the polyatomic alcohols as well as the oxyaldehydes (aldoles) and the oxyketones are lacking in hypnotic power, and this lack of power is proportional to the number of hydroxyl groups present. But the accumulation of alkyl groups about the carbon atoms which bear the hydroxyl groups seems to effect a compensation, or neutralizing of the action of the hydroxyl groups. Thus, some pinacones have been found to be active. Here again the favorable influence of the ethyl groups is clearly noticeable. For example, the dose of methyl pinacone,

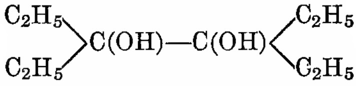


$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>C(OH)-C(OH)<\!\!\begin{matrix}CH_3\\CH_3\end{matrix}$$

required to produce sleep is 10 gms., while only 2 gms. are required in the case of methyl-ethyl pinacone,



and finally, only 1.5 gm. of ethyl pinacone,



In general, the effect of the hydroxyl group remains unaltered or at most only slightly modified when an alkyl group is substituted for the "typical" hydrogen atom, although such a substitution causes the substance to be more resistant toward the organism. Thus, in a very general way we can see a similarity in the action of ethers and acetals to the action of their fundamental compounds. But there is a series of important exceptions to this general rule which, however, concern chiefly the compounds of the aromatic series.

Aldehydes and Ketones

Even acetaldehyde shows a distinctly hypnotic action. This effect is exhibited in a greater degree by the polymeric paraldehyde $(C_2H_4O)_3$ which at the same time causes less preliminary excitation than the simpler body. The acetals are feeble sleep producers, and there is no appreciable difference in this respect between methylal and the ordinary acetal. Analogous to the difference in behavior of acetaldehyde and paraldehyde is the difference between the corresponding sulphur compounds, thioaldehyde and tri-thioaldehyde.

The influence of the substitution of halogens is again very prominently shown in these compounds. Trichloracetaldehyde, (Chloral) or rather, Chloral hydrate, which is easily formed by the addition of water, is a very strong narcotic. It was Liebreich who introduced this first synthetic therapeutic agent (chloral hydrate) and thereby gave a tremendous impulse to the modern synthesis of such substances. He thought that its action was dependent upon the splitting off of chloroform, a reaction which is easily accomplished outside the organism by means of alkaline liquids. Accordingly, he considered as useful hypnotics all those compounds which have three chlorine atoms, firmly enough bound to one carbon atom to make possible the formation of chloroform. Although this hypothesis resulted in such a beautiful practical success, it can hardly claim any advocates to-day. For it is very questionable whether there are at all appreciable quantities of chloroform produced in the organism from chloral hydrate. The larger part of it, as von Mering has showed, is converted into trichlorethyl alcohol, which conjugates with glucuronic acid, with the resultant formation of urochloralic acid or trichlorethylglucuronic acid ($C_2Cl_3H_2 \cdot C_6H_9O_7$). Trichlorethyl alcohol itself acts exactly like chloral. On the other hand, the trichloracetic acid obtained by the oxidation of chloral is said to be without hypnotic properties. Although there have been observations to the contrary, they have been attributed to impurities in the sodium trichloracetate used, a substance which it is exceedingly difficult to obtain in a pure state. Now trichloracetic acid will split off chloroform as easily as will chloral, and under similar conditions. So Liebreich's hypothesis must be considered untenable.

Chloral has certain disagreeable effects, especially an irritant action which depends upon the presence of the aldehyde group. Therefore, it was natural to make use of the capacity of this group for easy reaction and to prepare compounds which it was hoped would be devoid of these disagreeable side-effects. Such a series of derivatives has been made, and the results of an examination of these substances are interesting because they support the assumption that the aldehyde group participates in the action of chloral hydrate. For of these derived bodies the only ones which had the desired hypnotic action were those from which chloral could be easily reproduced. The more stable ones were not only less active as hypnotics, but were often strongly toxic. The result is that attempts in this direction have been fruitless, for in those cases where the desired hypnotic effect was attained the undesirable action of chloral, especially the effects upon the heart and respiration, was correspondingly pronounced. There are, however, some of the compounds which have the advantage of avoiding the disagreeable effect upon the stomach, because the chloral splits off in the lower parts of the digestive tract. We may thus classify the following from the compounds which have been prepared:

1. As sufficing for hypnotic effect:

Chloralamide, $CCl_3—CH(OH)—NH—CHO$, or more correctly chloral formamide, splits off chloral hydrate slowly in the organism.[1]

Chloralose or anhydro-gluco-chloral is a condensation product of chloral and glucose.[2]

The poison effects quite recently observed in the use of this substance are said to be due to the fact that there is formed beside the useful chloral, varying amounts of another substance, parachloralose, which has no hypnotic action, while it does produce nausea, rise in temperature, and a subsequent subnormal temperature.[1]

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[1] v. Mering, Therap. Monatsh., 1889, 565.

[2] Heffter, Ber., 22, 1050 (1889).

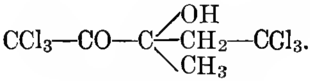
Very similar to this seems to be the case in the condensation products of chloral with pentoses.[2]

Dormiol or dimethyl-ethyl-carbinol-chloral is a condensation product of chloral and amylene hydrate.[3]

Hypnal or monochloral antipyrine.[4]

Compounds with the ortho forms, as

Chloran, an addition product of acetone-chloroform with chloral,



$$\mathrm{CCl_3{-}CO{-}C}\begin{matrix}\diagup\mathrm{OH}\\ -\mathrm{CH_2{-}CCl_3.}\\ \diagdown\mathrm{CH_3}\end{matrix}$$

2. As insufficient for hypnotic effect:

Chloral ammonium, or trichloraminoethyl alcohol, $CCl_3 \cdot CH(NH_2)OH$.[5]

Chloralimide, $CCl_3 \cdot CH{=}NH$.

Chloralcyanohydrate, $CCl_3 \cdot CH(OH)CN$, which decomposes with difficulty with the formation of hydrocyanic acid.

Chloral acetone, $CCl_3 \cdot CH(OH) \cdot CH_2 \cdot CO \cdot CH_3$.[6]

Monochlorurea and *dichlorurea*.

Chloralurethane, $CCl_3 \cdot CH(OH)NH \cdot CO_2 \cdot C_2H_5$.

Chloral acetophenone, $CCl_3 \cdot CH(OH) \cdot CH_2 \cdot CO \cdot C_6H_5$, which is converted in the organism to trichlorethylidene-acetophenone, $CCl_3 \cdot CH{=}CH \cdot CO \cdot C_6H_5$.

Chloral acetophenoneoxime.

Of the higher homologues of chloral the butyl chloral,

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[1] Mosso, Chloralosio e Parachloralosio, Genoa, 1894.

[2] Henriot and Richet, Semaine médic., 1894, No. 70.

[3] Fuchs and Koch, Münch. med. Wochschr., 1898, No. 37.

[4] Hertz, Therap. Monatsh., 1890, 243.

[5] Nesbitt, Therap. Gaz., 1888, p. 88.

[6] Königs, Ber., **25**, 794 (1892).

$CCl_3 \cdot CH_2 \cdot CH_2 \cdot CHO$, acts very much like ordinary chloral. A condensation product of this body with pyramidone which, put upon the market under the name of Trigemin, has been recommended by Overlach for use in cases of neuralgia, especially neuralgia of the trigeminus.

The ketones in general possess hypnotic properties, which appear most distinctly and prominently emphasized above the side-effects when there is an ethyl group in the compound. Thus, dimethyl ketone causes, coincident with a hypnosis like that observed in drunkenness, an excitation of the heart and a subsequent paralysis of the central nervous system. But diethyl ketone is a real and correct sleep producer with no effect whatever on the heart action. Similar, but less pronounced, is the action of dipropyl ketone. The aromatic ketones, such as benzophenone, act less powerfully than the aliphatic ketones, and, ranking between the two in physiological activity, as we should expect, are the mixed ketones of the type of acetophenone. And in this series of compounds the intensity of the action is essentially determined rather by the nature of the aliphatic component group than by the aromatic group. According to Fuchs and Schultze[1] the ketoximes are more intense in hypnotic action than the related ketones; but they have at the same time a harmful effect upon the digestive system.

Acids and Their Derivatives

The fatty acids exhibit a hardly perceptible narcotic action. Here, as in other cases, the carboxyl seems to reduce the effect of the compound. For when this group is replaced, as by an alkyl or by an amide group, the action is again more pronounced. There is to be observed in this case, again, within certain limits, an increase of effect with increased carbon content. Thus for example, certain esters and amides of valerianic acid are more active than the corresponding derivatives of acids of lower molecular weight. Hans Meyer[1] was the first to establish in the case of the aliphatic acid amides the fact that their physiological activity increased with their molecular weight and that at the same time the compounds increased in solubility in ether and fat. According to Harrass,[2] the administration of amides is accompanied not only by a narcotic effect, but also by phenomena similar to the spasmodic cramps caused by ammonia, which latter, however, are certainly not due to the ammonia component alone. Both effects are increased by alkylation on the nitrogen. The only compound of this sort that has come into practical use is valerianic acid diethylamide, which is marketed under the name of Valyl. The introduction of alkyl groups upon the carbon atom of acetanilide results in only slightly active bodies; but if at the same time the third hydrogen atom is replaced by a halogen (e.g. bromine) there are formed some very effective sleep producers, such as diethylbromacetamide, ethylpropylbromacetamide, and dipropylbromacetamide. The diethyl compound,

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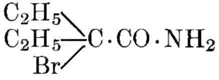
[1] Fuchs and Schultze, Münch. med. Wochschr., **51**, 1102 (1905).



$$\left.\begin{matrix} C_2H_5 \\ C_2H_5 \\ Br \end{matrix}\right> C \cdot CO \cdot NH_2$$

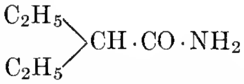
is used under the name of Neuronal.[3]

[1] H. Meyer, Arch. exp. Path. Pharm., **42**, 109 (1899).

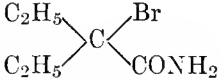
[2] P. Harrass, Arch. intern. Pharmacodyn., **11**, 431 (1903).

[3] Fuchs and Schultze, Münch. med. Wochschr., **51**, 1102 (1905).

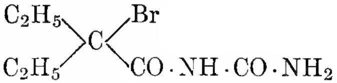
Under the name Adalin there has been introduced brom-diethylurea, which is recommended as a sedative and mild hypnotic, harmless to the heart and respiration in therapeutic doses. Such an action could have well been predicted for this compound. Although the general hypnotic action of the aliphatic compounds disappears when carboxyl is introduced, it reappears when this group is covered by an alkyl or amide group. Now the two things which increase this effect are the accumulation of alkyl, especially ethyl groups, and the introduction of halogen. Thus, although di-ethyl-acetamide,



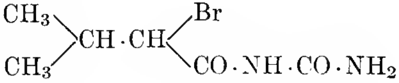
is too weak to be therapeutically useful, if bromine is introduced in place of the remaining hydrogen, we have Neuronal,



which can be utilized as a hypnotic. It is to be noted, too, that in general the urea derivatives are more powerful than the ammonia derivatives. Brom-diethyl-acetyl-urea,



has the same relationship to Neuronal that urea has to ammonia. Another representative of the group is Bromural, which is an α-brom-isovalerianyl urea,

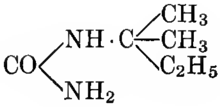


This is constitutionally different from Adalin in that the bromine is attached to a different carbon atom from that which carries the alkyl groups. Now in general the methyl groups have less effect than ethyl; but the active dose of Bromural is no greater than that of Adalin.

So we may be safe in saying that the location of the bromine seems not to be of great importance— or at least there is no one location which is essential.

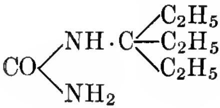
These compounds are valuable additions to our therapeutic agents in that they are efficient but mild sleep producers without particular anæsthetic action, and are said to be well tolerated in cases of cardiac disease.

In the case of carbamide the alkylation of the nitrogen may result under proper conditions in bodies with distinctly narcotic properties. As in the alcohol series we again see here the significance of the tertiary alkyl group. Although ureas into which have been introduced one or even more primary alkyl groups are lacking in physiological activity, nevertheless the tertiary bodies are strongly active—as for example tertiary amyl urea,



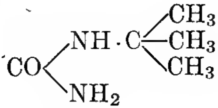
$$CO\left\langle\begin{matrix} NH\cdot C\left\langle\begin{matrix}CH_3\\ CH_3\\ C_2H_5\end{matrix}\right. \\ NH_2\end{matrix}\right.$$

and the tertiary heptyl urea which is very similar in structure,



$$CO\left\langle\begin{matrix} NH\cdot C\left\langle\begin{matrix}C_2H_5\\ C_2H_5\\ C_2H_5\end{matrix}\right. \\ NH_2\end{matrix}\right.$$

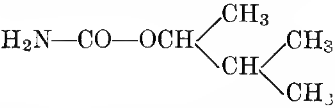
but more powerfully active. The tertiary butyl urea, on the other hand,



$$\mathrm{CO}<\begin{matrix}\mathrm{NH\cdot C}\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\\ \mathrm{NH_2}\end{matrix}$$

is much less active. Therefore, we notice in these series again the influence on the one hand of the accumulation of alkyl groups and on the other hand the effect of increasing the weight of these alkyl groups. Later we shall return for a consideration of the urea derivatives of alkylated acids (Veronal group).

With the urethanes, $H_2N \cdot CO \cdot OR$ we find a narcotic effect by action upon the central nervous system with the great advantage that all the important body functions are undisturbed. Again in this series, more noticeably in the lower members, the intensity of effect increases with the molecular weight of the substituting alcohol.[1] The introduction of the acetyl into the amino group reduces the toxicity of the compound. The activity is greater in certain urethanes of secondary alcohols, and again we must emphasize the effect of increasing the number of alkyl groups present as, for example, in the case of methylisopropylcarbinol urethane,



$$\mathrm{H_2N{-}CO{-}OCH}<\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH}<\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\end{matrix}$$

which is sold under the name of Hedonal.[2]

Nitro compounds possess general toxic properties that are manifested in different ways. The nitrous acid esters, which are isomeric with them, are so essentially and characteristically different in their physiological action that this action may be used for purposes of differentiation in cases of doubtful isomerism. This characteristic action consists of a dilation of the blood vessels. But there are observed differences of action which cannot be explained by constitutional peculiarities or carbon content, and are probably due to varying decomposition products.

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[1] Binet, Rev. médic. de la Suisse rom., 1893, 540, 628.

[2] Dreser, Wien. klin. Wochschr., **12**, 1007 (1899).

Even more marked are the differences in behavior observed in isomers of the cyanide compounds. Hydrocyanic acid, which we may consider an isocyanide, with perhaps divalent carbon $HN{=}C$, is about five times as toxic as dicyanogen $N{\equiv}C{-}C{\equiv}N$; but the characteristics of the effect are the same for both—that is, paralysis of the respiratory center in the medulla oblongata. Closely related to hydrocyanic acid are the organic isocyanides (isonitriles or carbylamines) $R{-}N{\equiv}C$ or $R{-}N{=}C$. According to Calmels,[1] methyl isonitrile is more poisonous than anhydrous hydrocyanic acid, while the ethyl compound shows a decided diminution in toxicity, being only about one-eighth as poisonous.

The nitriles $R{-}C{\equiv}N$, on the other hand, although also poisonous, are essentially different in action from hydrocyanic acid. Acetonitrile inhibits the reflex excitation and acts on some animals by inhalation as an anæsthetic. Brissemoret[2] states that the only excitation is in the stomach and intestinal tract. According to Verbruegge[3] the toxicity of these compounds increases with their molecular weight.

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[1] Calmels, Compt. rend., **98**, 536 (1884).

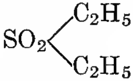
[2] A. Brissemoret, Soc. de biol., **60**, 54 (1906).

[3] Verbruegge, Arch. intern. Pharmacodyn., **5**, 161; Reid Hunt, ibid., **12**, 447.

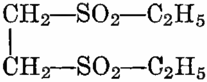
In the cyanic acid compounds and thiocyanic compounds isomerism does not result in any essential differences of effect. Their action is somewhat similar to that of hydrocyanic acid, but very much weaker. The derivatives which contain oxygen seem to be more poisonous than the corresponding sulphur compounds. We may remark here, too, that in some instances the esters show toxic effects which are barely perceptible or not at all noticeable in the free acids and in their metal salts.

Cyanogen in complex compounds seems to manifest its toxic effect only when there is a possibility of splitting off hydrocyanic acid in the organism, as, for example, in the case of sodium nitroprusside.

We have repeatedly called attention to the influence which the accumulation of alkyl groups has upon the sleep-producing effect of substances. We have also noted the superiority of the ethyl over the methyl group in such compounds. Both of these points are again plainly brought out by the action of the group of sulphones. Their effect was at first accidentally discovered by Baumann and Kast [1] but was later subjected to a scientific investigation with the following results: Monosulphones, such as diethylsulphone,



are inactive. The same is true of disulphones when the sulphone groups are attached to different carbon atoms, as in the case of ethylene diethylsulphone,



$$\begin{array}{l} CH_2{-}SO_2{-}C_2H_5 \\ | \\ CH_2{-}SO_2{-}C_2H_5 \end{array}$$

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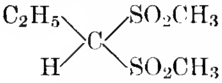
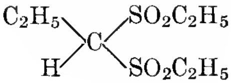
[1] Baumann and Kast, Z. physiol. Chem., 14, 52 (1890).

But when the two sulphone groups are attached to the same carbon atom there is a hypnotic effect, and this effect is increased as ethyl groups are added.

Dimethylsulphonethylmethane,

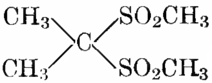


shows a slight action, while diethylsulphonethylmethane,

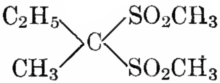


has a powerful hypnotic action, but at the same time a toxic effect. This latter effect disappears when the hydrogen of the central carbon atom is replaced by an alkyl group.

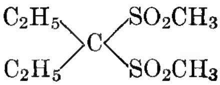
Dimethylsulphondimethylmethane,



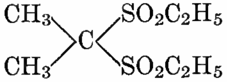
has practically no hypnotic action, while dimethylsulphonethylmethylmethane,



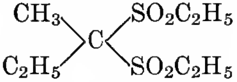
has a slight effect. The two isomers, dimethylsulphondiethylmethane,



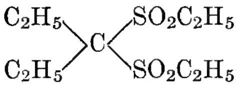
and diethylsulphondimethylmethane (Sulphonal),



act equally powerfully, while diethylsulphonethylmethylmethane (Trional),



is more powerful and, of course, the strongest of all the members of the series is diethylsulphondiethylmethane (Tetronal),



Now, quite in accord with our observations in other series, we find again that the replacement of the methyl group of sulphonal by alkyl groups containing more carbon atoms renders the body more powerfully active. We find the n-butyl is more active than iso-butyl. On the other hand, the action is arrested by the introduction of hydroaromatic and of aromatic groups and when two aromatic groups enter the same carbon atom, then, according to Hildebrandt,[1] the compounds become strongly toxic. The entrance of carboxyl or an amino group into the molecule of sulphonal also checks the hypnotic action of the compound, according to Th. Posner.[2]

Particularly interesting is the law proposed by Baumann for this series of compounds. He claims that the action of the sulphones depends upon the ease with which they can be decomposed in the organism. But he says that this decomposability cannot be tested out in vitro. For it has been found that those very members of the series which are most easily attacked by chemical reagents will pass entirely undecomposed through the organism, while, on the other hand, those members of the series which are most resistant to reagents in vitro are decomposed in the body.

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[1] Hildebrandt, Arch. exp. Path. Pharm., **53**, 90 (1905).

[2] Th. Posner, Chem. Ztg., **29**, 1107 (1905).

The Aromatic Series

In the aromatic hydrocarbons there is only a slight indication of narcotic action. Their predominant effect is cramp excitant and paralytic. They also cause, according to Baglioni,[1] clonic spasms. These, however, are not preceded, as in the case of the phenols, by a stage of increased excitation, but on the contrary, by a state of profound paralysis.

Chassevant and Garnier[2] established in the case of guinea-pigs three predominating symptoms of effect upon the nerves. These are cramps, muscle hypotonism, and hypothermism. Of these, the lowering of the heat production is a constant one observed from all derivatives, while the two other symptoms are variable.

In the homologues of this series there is to be observed a great variation of the toxic effect, depending upon the kind and number of alkyl groups present. Methyl benzol (toluol), and ethyl benzol are more poisonous than benzol itself; but isopropyl benzol (cumol) is less poisonous. Repeated alkylation diminishes the toxic effect so that we find, for example, in benzol and its methyl derivatives the following rising scale of toxicity:

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[1] Baglioni, Z. allgem. Physiol., **3**, 312 (1904).

[2] Chassevant and Garnier, Arch. intern. Pharmacodyn., **14**, 93 (1905).

Trimethyl benzols (mesitylene, pseudocumol)→dimethyl benzols (xylols)→benzol→methylbenzol (toluol). Among the xylols the toxic effect rises from the ortho to the meta and para compounds.

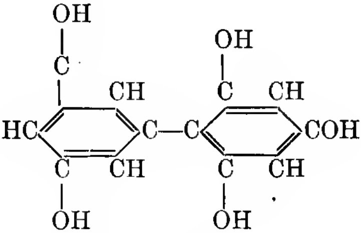
Naphthalene causes a retardation of the respiration, a depression of the temperature in cases of fever (but not normally), an increase of blood pressure in small doses, but a reduction of blood pressure in large doses.

Contrary to the case of the aliphatic series, where the substitution by halogens exerted a very powerful influence, it is almost without significance in the aromatic compounds.

The introduction of hydroxyl groups in these aromatic hydrocarbons increases the cramp-producing action. In some cases, as for example, phenanthrene, it may be almost entirely lacking in the hydrocarbon, but appear very distinctly in the hydroxyl derivative. At the same time, however, there is a change in the point of attack or action of the compound upon the organism. Benzol affects principally the brain, with a secondary action upon the cerebro spinal cord; but the phenols have quite the reverse action, affecting principally the cerebro spinal cord, while the action on the brain is very slight or almost lacking. So the phenols, since they increase the excitability of the motor mechanisms of the spinal cord, produce clonic spasms. Very large doses result further in paralyses (Baglioni).

Increasing the number of hydroxyl groups in this series has the same effect upon this cramp-producing activity that it had upon narcotic activity in the case of the polyatomic alcohols of the aliphatic series. That is, it gradually disappears as the number of hydroxyl groups is increased. Thus, the three dioxy benzols still cause cramps in frogs; but the trioxy benzols produce only convulsions or spasmodic contractions. On the other hand, the substances become much more toxic in another direction, which is manifested in a lethargy and in tremors.

Chassevant and Garnier,[1] however, state that the dioxy benzols are more poisonous than the phenols, while the trioxy benzols are less poisonous. According to Meyer,[2] Phloroglucide,



is without pharmacodynamic effect.

The degree of toxicity in the several series depends very largely upon the position of the substituting groups. In case of the dioxy benzols it rises from hydroquinone to resorcine to pyrocatechine.

In the organism, phenol is converted by synthesis into phenol sulphuric acid and phenyl-glucuronic acid, and also it condenses with partial oxidation to form dioxybenzols (pyrocatechin and hydroquinone sulphuric and glucuronic acids). The same is true for the homologues and substitution products.

The action of naphthols is entirely analagous to that of the phenols. Of the oxyderivatives of the higher hydrocarbons, those of phenanthrene are of importance on account of their relationship to the alkaloids of the morphine group. As has already been mentioned, they cause cramp effects.

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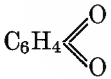
[1] Chassevant and Garnier, Soc. biol., **55**, 1584.

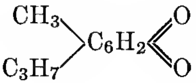
[2] See Herzig and Cohn, Wien. Monatsch., **29**, 677.

Similar to the behavior of the phenols is that of the quinones, as we should perhaps expect from the close chemical relationship. According to Brissemoret,[1] there are caused very excitant effects in the alimentary canal and on the outer skin by ordinary Quinone,



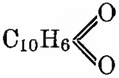
$$C_6H_4\begin{matrix}/\!/O\\ \backslash\!\backslash O\end{matrix}$$

Thymoquinone,



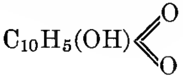
$$\begin{matrix}CH_3\diagdown\\ C_3H_7\diagup\end{matrix}C_6H_2\begin{matrix}/\!/O\\ \backslash\!\backslash O\end{matrix}$$

and Naphthoquinone,



$$C_{10}H_6\begin{matrix}/\!/O\\ \backslash\!\backslash O\end{matrix}$$

The same is true in the case of the natural product Juglon, which is oxynaphthoquinone,



$$C_{10}H_5(OH)\begin{matrix}/\!/O\\ \backslash\!\backslash O\end{matrix}$$

Somewhat the same properties are manifested in the purgative effects of various anthra-quinone derivatives.

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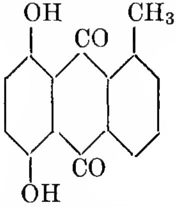
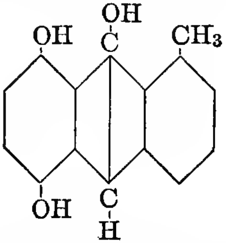
[1] Brissemoret, Soc. biol., **59**, 453 (1905); **60**, 175 (1906).

Chrysophanic acid



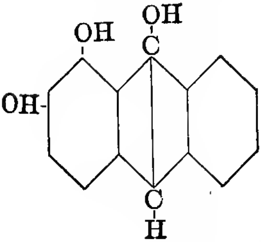
is found naturally in members of Rumex and Rheum species, as well as in the Cascara Sagrada.

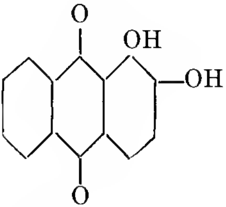
There is a closely related body which has found application in various affections of the skin. This is Chrysarobin,[1]



which, being a reduction product of chrysophanic acid, can easily be converted into that substance by oxidation. A similar relation holds between the related bodies

Anthrarobin and Alizarine





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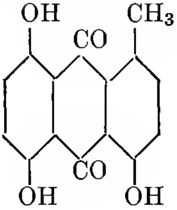
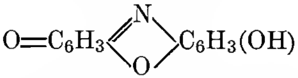
[1] Hess, Ann. Chem., **309**, 32 (1899).

Related to chrysophanic acid are the various emodines of rhubarb, the aloe species, cascara sagrada, etc. Thus the emodine of the Chinese rhubarb has, according to Hess[1] the following formula:



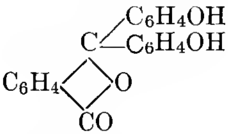
Brissemoret[2] is authority for the statement that the essential condition for the action of these oxymethyl anthraquinones is the presence of an oxygen atom in the quinone binding. Ordinary benzoquinone has a purgative effect as has also resorufine.



$$O{=}C_6H_3\langle\overset{N}{\underset{O}{}}\rangle C_6H_3(OH)$$

Accordingly, there does seem to be a necessity for at least one hydroxyl or quinone oxygen.

PHENOLPHTHALEIN



has, of course, been also found to be an effective purgative. Even more strongly purgative than the natural emodines are some of the synthetic polyoxyanthraquinones. It was found necessary for practical application, however, on account of the violent side-effects of these substances, to convert them into compounds which are only gradually decomposed in the intestinal tract. Thus, Purgatine is the diacetyl ester of anthrapurpurine,

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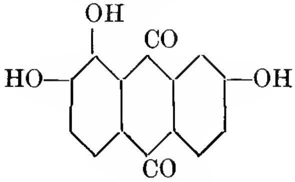
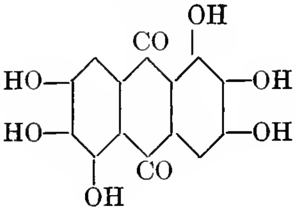
[1] Hesse, l. c.

[2] Brissemoret, Soc. biol., **55**, 48 (1903).



Exodine is a mixture of diacetyl-rufigallic-tetra-methyl ether, which acts only slightly, with the acetylpentamethyl ether, which by itself would have too violent an action.

Exodine



Two other substances whose action is so violent that it must be moderated for practical application are the diacetyl-rufigallic acid and the rufigallic acid tetramethyl ether. But if the hydroxyls are all completely closed by alkyl radicles as in the hexamethyl ether the compound is ineffective.[1]

In this connection we may mention that it is a general phenomenon that a given effect of a compound is diminished by the alkylation or acylation of the hydroxyl groups. The general effect is, of course, to make the compound less active chemically as well as pharmacologically. Thus we find that guaiacol,

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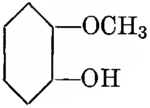
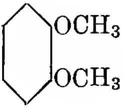
[1] Ebstein, Deut. med. Wochschr., **31**, 55 (1905).



has an effect similar to that of phenol and pyrocatechol, but less poisonous; the maximum dose being for man 1 gm. in the case of guaiacol and about one-tenth as great in the case of phenol. The toxicity, moreover, is still further diminished when the second hydroxyl group is also alkylated, as in the dimethyl ether Veratrol,



The introduction of acid groups into the phenolic hydroxyl does not essentially change the physiological character of the compounds as much as one might at first expect. The reason for this is that the derivatives so obtained are saponified in the organism and the hydroxyl group is again replaced. But the use of compounds of this sort has the advantage that the active substance comes into play gradually, that is, only as fast as the saponification proceeds. Moreover, since this saponification takes place for the most part in the intestines, the stomach and upper digestive tract are protected from any chance secondary effects.

In some cases, however, alkylation of the hydroxyl group does have the opposite effect. For example, the dimethyl ether of resorcine is much more toxic than resorcine itself. Dimethyl sulphate is much more toxic than sulphuric acid. Such rather exceptional phenomena may perhaps be explained by saying that the introduction of the alkyl group favors the selection of the substance by the sensitive membranes. And in the cases which we are now considering, such a selection must depend very largely upon a change in the physical conditions of the membranes themselves. In some other cases, moreover, we may have to deal not only with an increase in the main effect, but also with the removal of a disturbing influence which a hydroxyl, or particularly a carbonyl group, exerts upon the primary action of the substance.

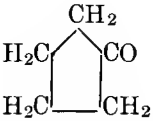
The influence of a carboxyl group quite generally appears in a retardation or inhibition of the primary effect of a compound. For example, when it enters an aromatic hydrocarbon it suppresses the action up to the point of causing a constant hypothermic effect, and too, it diminishes the toxic effect. If several carboxyl groups are attached to the nucleus, or if there are other substituted groups on the nucleus with the carboxyl group, then the strength of the carboxyl influence depends upon the relative position of these groups. This has already been shown in the case of the oxybenzoic acids. In the dibasic acids the toxicity diminishes from the meta to the para, to the ortho compounds, while in the toluic acids, according to Chassevant and Garnier it diminishes from the meta to the ortho to the para compounds.

The sulphonyl group possesses this inhibiting or retarding influence to a still more marked degree than the carboxyl group. This is very largely and fundamentally the reason for the failure of some compounds which have been prepared by introducing the sulphonyl group, in order to render easily soluble some effective but difficultly soluble substances.

Hydroaromatic Compounds

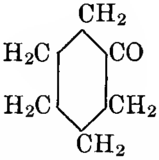
The general effect of ring-formed ketones is a paralysis of the central nerve system and the motor nerve terminals. The latter are more affected as the size of the ring is increased. Thus, the effect increases from pentanone or ketopentamethylene (I) to Hexanone or ketohexamethylene (II) to Suberone or ketoheptamethylene (III).[1]

I



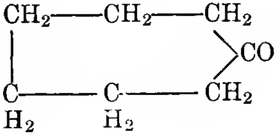
KETOPENTAMETHYLENE

II



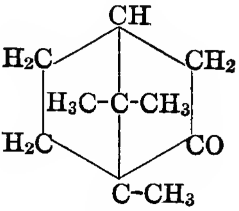
KETOHEXAMETHYLENE

III



KETOHEPTAMETHYLENE or CYCLOHEPTANONE

IV



CAMPHOR

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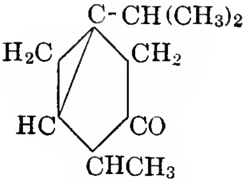
[1] Jacobi, Hayashi and Szubinski, Arch., exp. Path. Pharm., **50**, 199 (1903).

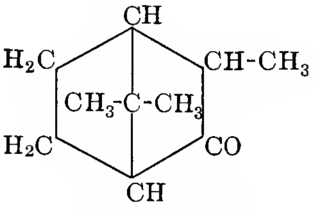
Camphor (IV), which is related to ketohexamethylene, has a cramp-excitant effect. It also stimulates the muscles of the heart to such an extent that it will neutralize the stoppage of heart action by muscarine in the case of the frog. In warm-blooded animals camphor also raises the blood pressure, even when the vasomotor nerve center is paralyzed by chloral hydrate.

V



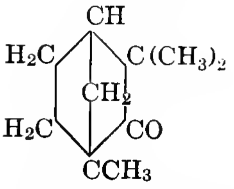
Thujone

VI



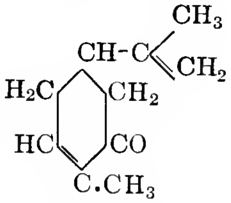
Fenchone (Wallach)

VII



Fenchone (Semmler)

VIII



Carvone

The behavior of Thujone (V) is similar to that of camphor, but Fenchone[1] (which according to Wallach has the constitution VI but according to Semmler has the constitution VII) and Carvone VIII[2] have a different action. Carvone is a poison which has a violent cramp-producing action, which may perhaps be attributed to the double bond in the ring. A reason for ascribing this action to the double bond is that such an effect does not occur, for Menthone (IX) which is keto-hexahydro-*p*-cymene, nor for Pulegone X.

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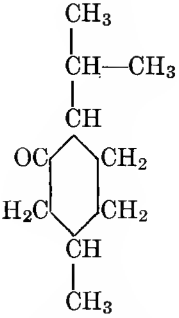
[1] Matzel, Arch. intern. pharmacodyn., **15**, 331 (1905).

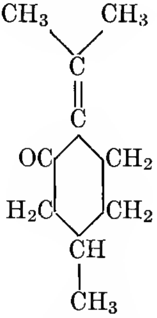
[2] Hildebrandt, Z. physiol. Chem., **36**, 441 (1902).

IX



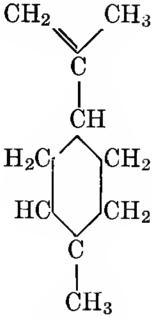
Menthone

X



Pulegone

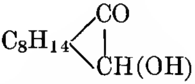
XI



Limonene

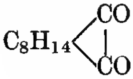
Nevertheless we must admit that the carbonyl group plays a very essential part in the physiological action, for we find only a very slight toxicity in Limonene (XI) which is quite similarly constituted except that the carbonyl group is missing.

Of the camphor derivatives, we find that monobrom camphor, as well as the oxidation products formed within the organism, show a cramp effect. On the other hand we do not find this effect in oxy-camphor.



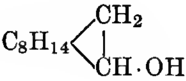
$$C_8H_{14}\left\langle\begin{matrix}CO\\ |\\ CH(OH)\end{matrix}\right.$$

which is a reduction product of camphor-quinone



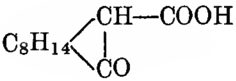
$$C_8H_{14}\Big\langle\begin{matrix}CO\\ |\\ CO\end{matrix}$$

nor do we find it in borneol



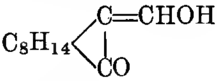
$$C_8H_{14}\Big\langle\begin{matrix}CH_2\\ |\\ CH\cdot OH\end{matrix}$$

According to Pouchet and Chevalier[1] however, borneol and its esters (especially the iso-valerianate, which is in use under the name of Bornyval) have an effect upon the circulatory system similar to that of camphor. We find also that when the carboxyl group is introduced into this otherwise unchanged molecule with the formation of camphor carboxylic acid



$$C_8H_{14}\Big\langle\begin{matrix}CH\text{—}COOH\\ |\\ CO\end{matrix}$$

the specific cramp effect is inhibited. It is a very remarkable fact that oxymethylene camphor



$$C_8H_{14}\Big\langle\begin{matrix}C{=}CHOH\\ |\\ CO\end{matrix}$$

shows no cramp effect, but paralyzes the central nerve system and heart; but oxyethylidene camphor and oxypropylidene camphor again show the typical cramp effect. This may be explicable by the fact that the acid character of the first compound is vanishing in the high homologues.[1]

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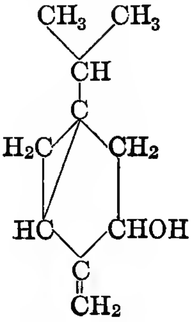
[1] Pouchet and Chevalier, Bull. gen. de Therap., **149**, 828 (1905).

According to Hildebrandt[2] Sabinol XII



SABINOL

in spite of its close relationship to Thujone (V) has an effect different from all the other camphor-like bodies in that it causes hæmoglobinuria and methæmoglobinuria.

In this connection a fact established in several cases by Hildebrandt[3] is particularly interesting, because it is in contradiction to the condition found in other groups. This is the fact that chain-form isomers of cyclic camphors are the more powerful. For example we may cite citral as compared with cyclocitral, nerol and geraniol as compared with cyclogeraniol.

Concerning the influence of stereoisomerism there are somewhat divergent opinions. In the case of the stereoisomers of camphor the qualitative similarity of effect is universally acknowledged. According to Langguard and Maass[1] the excitant action of lævo camphor is even greater than that of the natural dextro camphor, and racemic camphor is intermediary; but we find a more recent statement, and we must confess a more improbable statement, by Hämäläinen[2] that the racemic and dextro forms have nearly the same activity while the lævo compound is considerably weaker in effect.

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[1] Bruhl, Ber., **37**, 2179 (1904).

[2] Hildebrandt, Arch. exp. Path. Pharm., **45**, 150 (1901).

[3] Ibid., Neuere Arzneimittel, p. 145 ff.

Inner Disinfection

As is very well known, the phenols derive a special importance from the fact that they exert powerfully toxic effects upon the lower life forms (bacteria), that is, a so-called antiseptic action. In order to combat infectious diseases, as well as for prophylactic use, it would be highly desirable to be able to employ powerful internal disinfectants. But the unfortunate situation is that there is quite generally associated with the destructive action upon unicellular organisms a toxic effect upon the higher organisms also. And changes in the compounds which decrease the toxicity toward the higher form have the deplorable result of lessening the antiseptic properties of the substances. Thus, by the introduction of the carboxyl group into the phenol the toxicity is greatly reduced, especially if the introduction is in the meta or para position. But the ortho hydroxy acid (salicylic acid) is still more toxic than benzol and benzoic acid. Of the three isomers, then, salicylic acid alone still retains a rather considerable power for disinfection, and this is considerably lowered in comparison with phenol.

---

[1] Langguard and Maass, Therap. Monatsh., Nov., 1907.

[2] Hämäläinen, Chem. Zentr., 1908, II, 1451.

Change in compounds.	Disinfection power.	Toxic effect.
Introduction of halogen (Cl, Br).	Increased, corresponding to the number of halogen atoms. Sixteen (16) molecules of tetrachlorphenol, or, 2 molecules of pentabromphenol are equivalent to 1000 molecules of phenol.	At first diminished, then increased. For tri-halogen compounds it is about the same as that of phenol. Rises strongly for further substituted bodies. The cramp effect is diminished with increased halogen content and finally stops.
Introduction of alkyl groups in the presence of halogen in the molecule.	Increased. Tri-brom-*m*-xylenol is twenty times as active as tri-bromphenol. Tetra-brom-*o*-cresol is sixteen times as active as tetra-chlor-phenol.	Compensates the toxic effect of the halogen. Tetra-brom-*o*-cresol has very little toxic action.
Combination of two phenols.		
Direct (bi-phenols).	Increased.	
By CH_2.	Increased.	
By CHOH.	Increased.	
By CHOR.	Increased.	
By CO.	Diminished.	
By SO_2.	Diminished.	

This relationship, however, does not hold universally and without exception. Thus, after alkylation in the benzol ring with the formation of cresol, we find the antiseptic action greater than in the case of the simple phenol, while the toxicity of the compound for higher life forms is increased only slightly, if at all. In fact, for a frog, all the cresols are less toxic than phenol. For warm-blooded animals para-cresol is more poisonous than phenol, while the ortho compound is about the same as phenol and meta-cresol is still less toxic, according to Tollens.[1]

The admirable investigations upon this subject by Bechhold and Ehrlich [2] disclosed the most varied changes in action by modifications of the compounds. These results are given in table on page 78 in so far as they have not been already treated.

It was found, however, in attempting a practical application of such compounds that the strong disinfectant power of the best disinfectants is very much modified in the blood serum. The result is that with these compounds, too, we must confess that inner disinfection has not been successful.

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[1] Tollens, Arch. exp. Path. Pharm., **52**, 220 (1905).

[2] Bechhold and Ehrlich, Z. physiol. Chem., **47**, 173 (1906).

NITROGEN COMPOUNDS

Ammonia and Its Simpler Derivatives

Disregarding the excitant and caustic action of the free bases, the characteristic effect of ammonia is a cramp effect which causes in mammals the excitation of various functional tracts of the spinal cord and its branches. There results a temporary inhibition of respiration, more pronounced in the cramp intermissions. Larger doses cause, subsequent to the excitation stage, a paralysis of the nerve centers that ends fatally. Immediately after the injection of ammonia, there is a direct stimulation of the heart and a consequently large increase in blood pressure. Then follows a period of smaller increase in blood pressure, caused by vascular contraction, due to a stimulation of the vasomotor nerve centers. At the same time there is a diminution in the pulse frequency, although during the first stage this is increased.

In frogs the characteristic effect is manifested by strong excitation indicated by a reflex cry; then there follow convulsions and tetanus, and finally general paralysis.

The replacement of hydrogen of ammonia by alkyl radicles immediately reduces the toxic action in a quite extraordinary manner. Moreover, the ammonia group, or all that remains of it, arrests the hypnotic action of the hydrocarbons. So we may consider the ammonia and alkyl radicles as mutually interfering groups. According to Hildebrandt[1] the toxic effect in secondary amines increases with increasing molecular weight.

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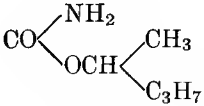
[1] Hildebrandt, Arch. exp. Path. Pharm., **54**, 125 (1905).

The physiological character of the compounds is, however, completely changed, as we shall see later in our discussion, when the alkylation is completed with the formation of quaternary ammonium bases.

When an acid group is introduced, the characteristic ammonia effect is reduced to an even more marked degree than is caused by alkylation. This is the case whether the ammonia group is in combination with the oxygen of the carboxyl or with carbon. Both the acid amides and the amino acids of the aliphatic series are in general physiologically inactive. The amino acids of the higher series are to be regarded as albumin builders, and therefore as belonging to the group of nutritive substances. An exception to the previous statement is found in carbamic acid, $NH_2—COOH$, which is poisonous. This acts as a cramp-producing poison in a manner similar to ammonia, but somewhat modified. The cause of this exception is perhaps to be found in the ease with which the compound is broken down. For as soon as we make it more resistant to decomposition by the esterification of the carboxyl, we have formed urethanes, which are scarcely poisonous bodies. Furthermore in these compounds, the original ammonia effect has been so reduced or neutralized that the hypnotic action of the alkyl radicle is able to assert itself, and the intensity of its effect depends upon the character of the alkyl group.[1] In other words the original action has been suppressed sufficiently for the newly introduced action to characterize the compounds. Thus, in methyl-propyl-carbinol urethane (Hedonal),

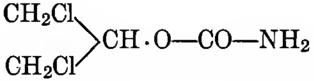


$$CO\left\langle\begin{array}{l}NH_2\\ OCH\left\langle\begin{array}{l}CH_3\\ C_3H_7\end{array}\right.\end{array}\right.$$

[1] Binet, Rev. médic. de la Suisse rom., 1893.

on find a useful, mild sleep producer, which leaves all the life functions unaffected.

A more recent compound which has been introduced under the name of Aponal is ethyl-dimethyl-carbinol urethane. This is probably still more powerful in action. It remains to be seen whether it possesses a diuretic action which has rendered the use of hedonal somewhat objectionable. These urethanes have, however, been claimed to possess a somewhat injurious action upon the heart and respiration. These effects, seem to have been satisfactorily overcome by a compound introduced as Aleudrin. This substance has, like Hedonal, the skeleton of isopropylurethane; but the alkyl groups are chlorinated,



$$\left.\begin{matrix}CH_2Cl\\ CH_2Cl\end{matrix}\right> CH\cdot O{-}CO{-}NH_2$$

The margin between the narcotic dose and the fatal dose is less for warm-blooded than for cold-blooded animals; but it is large enough for practical purposes. For man, sleep is produced by 0.5 gm. The body temperature, respiration, heart action and circulation are very little affected. Aleudrin appears to be a harmless sleep-producer of scientifically correct construction according to theoretical conceptions.

The essential part played by the acid radicle residuum in the neutralization of the primary toxic effect is very clearly shown by a comparison of the amino acids and urethanes with the closely related aminoacetals. Ordinary aminoacetal, $NH_2CH_2CH(OC_2H_5)_2$, produces a paralysis of the respiration in the same way that ammonia does.[1]

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[1] Mallèvre, Pflüger's Arch., 49, 484 (1891).

This, of course, is quite in contrast to the action of the methanes and amino acids.

Of peculiar interest is the action resulting from the conjugation of the ammonia residual group and the aromatic hydrocarbons, which are themselves cramp excitants. We observe then a change in the points of attack as compared with the action of ammonia. Aniline attacks not only the motor centers in the branches of the spinal cord, but also and more particularly those of the middle brain, where it causes first a passing excitation that manifests itself in convulsions, and then paralysis. The prominent symptoms are dizziness, drowsiness, and finally well-developed collapse. Aniline has the further effect of destroying the hæmoglobin. There is also with aniline another effect which is therapeutically exceedingly important and that is the diminution of the body temperature.[1]

As we have already seen, this action is peculiar to the aromatic ring; but it becomes pronounced only after certain substitutions have taken place.[2] It is lacking in naphthalene and phenanthrene derivatives. In fact, there is even a marked rise in temperature after the administration of tetra-hydro-β-naphthylamine.[3]

The other aromatic amines possess in a marked degree the injurious effects of aniline. The antipyretic effects are modified by the introduction of alkyl radicles into the molecule, the action depending largely upon whether the group enters in the ortho, meta, or para position. Thus, meta toluidine acts almost like aniline; but the ortho and para toluidines are very much weaker in action. The direct attachment of the amino group to the ring seems also to be of essential importance for the antipyretic effect. For example there is such an action in only a slight degree in the case of benzylamine, $C_6H_5—CH_2—NH_2$.

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[1] Cahn and Hepp, Zentr. klin. Med., 1886, No. 33.

[2] Cf. Fränkel, Arzneimittelsynthese, 2d ed., p. 241 ff.

[3] Stern s. Bamberger and Filehne, Ber., **22**, 777 (1889).

In the basic triphenyl methane dyestuffs the poison effect increases in a marked degree with the introduction of alkyl groups, especially if this introduction takes place on the nitrogen. This effect, however, is still weak enough in pararosaniline to permit its use in the therapeutic treatment of trypanosome diseases. The introduction of acid groups diminishes the poison action; but at the same time it also stops the trypanocidal power, as either the sulphonic or carboxyl group will entirely prevent this effect.[1]

Naturally the same substituting groups which weaken the effects of ammonia have a like effect upon aniline. The next logical step was to determine whether such a diminution of action would be more in a desirable or in an objectionable direction. If acid groups (carboxyl or especially sulphonyl) are introduced into the ring the action is weakened in both directions, but the poison effect is strongest in the ortho derivatives, and it is still further increased by introducing methyl in the amino group.[2]

The substitution of alkyl groups on the nitrogen has little effect, while acid groups have a quite noticeable effect. Thus, in the case of acetanilide (Antifebrin) the poison effect is sufficiently diminished and the antipyretic action sufficiently retained so that a practical application of the substance is possible. Nevertheless there remains enough of the ill effect to demand caution in its administration. The poisonous action is still further diminished in phenyl urethane (Euphorine), $C_6H_5NHCOOC_2H_5$; but the antipyretic efficiency is rather low. The aniline action is still further diminished in both directions in such cases as acetanilido acetic acid,

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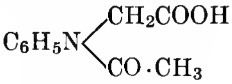
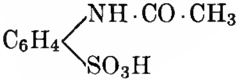
[1] Ehrlich, Berl. klin. Wochschr., 44, 223 ff. (1907).

[2] Hildebrandt, Hofmeister's Beitr., 7, 433 (1905).



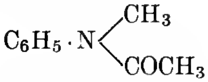
$$C_6H_5N{<}\begin{matrix}CH_2COOH\\ CO\cdot CH_3\end{matrix}$$

and acetyl sulphanilic acid and its salts (Cosaprine being the sodium salt),



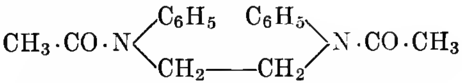
$$C_6H_4{<}\begin{matrix}NH\cdot CO\cdot CH_3\\ SO_3H\end{matrix}$$

Methyl acetanilide (Exalgine),



$$C_6H_5\cdot N{<}\begin{matrix}CH_3\\ COCH_3\end{matrix}$$

is less desirable than acetanilide, but the nearly related diacetyldiphenylethylenediamine,



$$CH_3\cdot CO\cdot N{<}\begin{matrix}C_6H_5 & C_6H_5\\ CH_2 - & - CH_2\end{matrix}{>}N\cdot CO\cdot CH_3$$

is said to be less violent.[1]

Now it has been shown by the investigations of Schmiedeberg[2] that aniline and its derivatives are rendered harmless by the organism by the introduction of an hydroxyl group in a position para to the amino group. Paraaminophenol is much less poisonous than aniline, although it does cause the formation of methæmoglobin. This effect is somewhat but not sufficiently reduced by the introduction of an acetyl group. Only when the hydroxyl is esterified do we attain a point where the preparation is adapted for therapeutic use. The type of this sort of a compound is acetyl-*p*-amidophenol ethyl ether or para-ethoxy acetanilide (Phenacetine),

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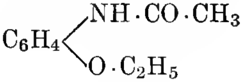
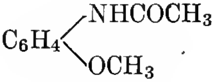
[1] Grassmann, Bull. soc. ind. Mulh., 1907, 4.

[2] Schmiedeberg, Arch. exp. Path. Pharm., 8, 1 (1878).



$$C_6H_4\begin{cases}NH\cdot CO\cdot CH_3\\ O\cdot C_2H_5\end{cases}$$

Numerous derivatives have been prepared from phenetidine, the base of phenacetine, as well as from Anisidine, which is the base of Methacetine,

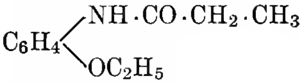


$$C_6H_4\begin{cases}NHCOCH_3\\ OCH_3\end{cases}$$

the lower homologue of phenacetine. Such bodies have been subjected to careful physiological examination; but we will mention here only some of the preparations derived from phenacetine:

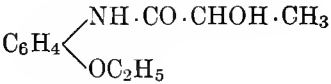
1. Compounds derived by replacing the acetyl with other acid groups:

Propionyl derivative (Triphenin),



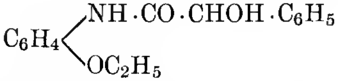
$$C_6H_4\begin{cases}NH\cdot CO\cdot CH_2\cdot CH_3\\ OC_2H_5\end{cases}$$

Lactyle derivative (Lactophenin),



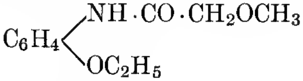
$$C_6H_4\begin{cases}NH\cdot CO\cdot CHOH\cdot CH_3\\ OC_2H_5\end{cases}$$

Mandelic acid derivative (Amygdophenin),



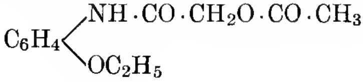
$$\mathrm{C_6H_4}\left\langle\begin{array}{l}\mathrm{NH\cdot CO\cdot CHOH\cdot C_6H_5}\\ \mathrm{OC_2H_5}\end{array}\right.$$

Methylglycolic acid derivative (Kryofin),



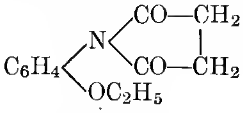
$$\mathrm{C_6H_4}\left\langle\begin{array}{l}\mathrm{NH\cdot CO\cdot CH_2OCH_3}\\ \mathrm{OC_2H_5}\end{array}\right.$$

Acetylglycolic acid derivative,



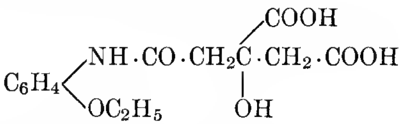
$$\mathrm{C_6H_4}\left\langle\begin{array}{l}\mathrm{NH\cdot CO\cdot CH_2O\cdot CO\cdot CH_3}\\ \mathrm{OC_2H_5}\end{array}\right.$$

Succinic acid derivative (Pyrantin),



$$\mathrm{C_6H_4}\left\langle\begin{array}{l}\mathrm{N}\left\langle\begin{array}{l}\mathrm{CO{-}CH_2}\\ \qquad\;\;\vert\\ \mathrm{CO{-}CH_2}\end{array}\right.\\ \mathrm{OC_2H_5}\end{array}\right.$$

Citric acid derivative (Apolysin),



$$\mathrm{C_6H_4}\left\langle\begin{array}{l}\mathrm{NH\cdot CO\cdot CH_2\underset{OH}{\overset{COOH}{C}}\cdot CH_2\cdot COOH}\\ \mathrm{OC_2H_5}\end{array}\right.$$

The preparation which has been advertised under the name of Citrophene as citric acid triphenetidide is according to Hildebrandt[1] essentially a citric acid salt of phenetidine.

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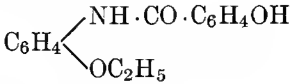
[1] Hildebrandt, Zentr. inn. Med., **16**, 1089 (1895).

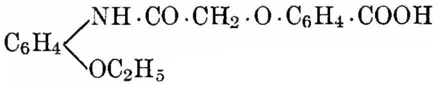
Salicylic acid derivatives:

(*a*) Salicylphenetidide,



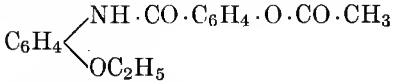
$$\mathrm{C_6H_4}\left\langle\begin{matrix}\mathrm{NH\cdot CO\cdot C_6H_4OH}\\ \mathrm{OC_2H_5}\end{matrix}\right.$$

(*b*) Salicylic acetic acid derivative (Phenosal),



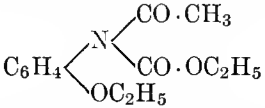
$$\mathrm{C_6H_4}\left\langle\begin{matrix}\mathrm{NH\cdot CO\cdot CH_2\cdot O\cdot C_6H_4\cdot COOH}\\ \mathrm{OC_2H_5}\end{matrix}\right.$$

(*c*) Acetyl salicylic acid derivative,



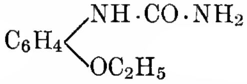
$$\mathrm{C_6H_4}\left\langle\begin{matrix}\mathrm{NH\cdot CO\cdot C_6H_4\cdot O\cdot CO\cdot CH_3}\\ \mathrm{OC_2H_5}\end{matrix}\right.$$

Acetyl-ethyl carbonic acid derivative (Thermodin),



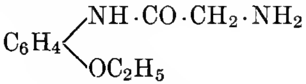
$$\mathrm{C_6H_4}\left\langle\begin{matrix}\mathrm{N}\left\langle\begin{matrix}\mathrm{CO\cdot CH_3}\\ \mathrm{CO\cdot OC_2H_5}\end{matrix}\right.\\ \mathrm{OC_2H_5}\end{matrix}\right.$$

Amino carbonic acid derivative (Dulcin),



$$\mathrm{C_6H_4}\left\langle\begin{matrix}\mathrm{NH\cdot CO\cdot NH_2}\\ \mathrm{OC_2H_5}\end{matrix}\right.$$

Amino acetic acid derivative (Phenocoll),



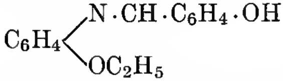
$$\mathrm{C_6H_4}\left\langle\begin{matrix}\mathrm{NH\cdot CO\cdot CH_2\cdot NH_2}\\ \mathrm{OC_2H_5}\end{matrix}\right.$$

2. Compounds derived by introducing acid groups in the ring (for the purpose of obtaining easily soluble bodies):

Phenacetine sulphonic acid. Phenacetine carbonic acid.

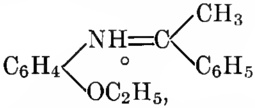
3. Compounds obtained by condensation with aldehyde and ketones:

with salicylic aldehyde (Malakin),



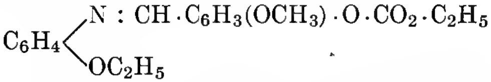
$$C_6H_4\left\langle\begin{array}{l}N\cdot CH\cdot C_6H_4\cdot OH\\ OC_2H_5\end{array}\right.$$

with acetophenone (the citric acid salt is Malarine),



$$C_6H_4\left\langle\begin{array}{l}NH{=}C\left\langle\begin{array}{l}CH_3\\ C_6H_5\end{array}\right.\\ OC_2H_5,\end{array}\right.$$

with vanillin ethyl carbonate (Eupyrine),



$$C_6H_4\left\langle\begin{array}{l}N : CH\cdot C_6H_3(OCH_3)\cdot O\cdot CO_2\cdot C_2H_5\\ OC_2H_5\end{array}\right.$$

From an examination of these substances and similar preparations, and an observation of their physiological action, it has been possible to generalize somewhat and formulate some regularities in their action. In the first place, considering the substitution of the amino group of amino phenol by an acid radicle, this must be firmly enough bound so that it is not split off by the acid of the gastric juice (which amounts to two per cent hydrochloric acid). For if this happens there appear at once the undesirable and poisonous effects of para-phenetidine. On the other hand the binding of such an acid radicle must not be too firm. For it has been found that the only substances of this group which have a good antipyretic action are those whose ingestion causes the appearance of the indophenol reaction in the urine. This color reaction which results from the action of α or β naphthol upon bodies with an amino group indicates that the substances ingested must be capable of being broken down in the organism to compounds which have such a free amino group (for example para-aminophenol from para-amidophenetol or para-phenetidine).[1] And observation has justified the conclusion that the intensity of the antipyretic effect is within certain limits proportional to the amount of para-aminophenol which is split off in the organism. It is obvious, then, that too slow a process of splitting up the compound will result in failure of the desired effect. This was the result and its cause when the attempt was made to use a combination with salicylic acid, a compound which has its own antipyretic and antineuralgic properties and therefore gave hope of forming particularly active preparations. The mandelic acid derivative is an example of another class of failures. The fundamental reason is the same—that is, there is too little splitting down of the compound in the organism; but the reason in this case is the slight solubility of the substance in the stomach and intestinal tract and the consequent insufficient resorption.

So far as substitution of the hydroxyl group by alkyl radicles is concerned it does not pay to go higher than the ethyl group, as the antipyretic effect diminishes with the higher alkyl radicles. In fact the ethyl ether is somewhat less active in this respect than the methyl compound; but the difference is so slight that it is more than offset by the desirable and very considerable diminution of the toxic effect.

If we start with a body such as acetyl-*p*-amino phenol, which has a free hydroxyl group, and replace by an alkyl radicle the hydrogen which is still attached to the nitrogen, the result is a series of inactive compounds. But if at the same time we alkylate the hydroxyl also, then there is observed a narcotic effect, which is barely suggested in the parent body. In this respect the methyl and ethyl derivatives behave about alike, and with a further increase in the magnitude of the alkyl radicle all the effects seem to diminish.[1]

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[1] Treupel and Hinsberg, Arch. exp. Path. Pharm., **51**, 262 (1904).

An antipyretic effect is also to be observed in the urea derivatives of anisidine and phenetidine. The phenetidine compound, which is para-ethoxy-phenyl carbamide, is particularly distinguished by an intensely sweet taste and has therefore been called Dulcin. This sweet taste is found in neither the lower compound (the methoxy body) nor in the higher homologues.[2]

An effect similar to that of phenacetine, but weaker, is found with the isomeric compound acetyl-ortho-phenetidine.

Of the diamines the aliphatic bodies such as tetramethylenediamine (Putrescine), $NH_2—(CH_2)_4—NH_2$, and pentamethylenediamine (Cadaverine), $NH_2—(CH_2)_5—NH_2$ are physiologically entirely inactive. In some derivatives in which one or both of the amino groups have been converted into imino groups by means of negative substituents there appear strong toxic effects.

Thus, for example, in the formaldehyde derivative of Cadaverine and in Sepsine prepared by Faust[3] this effect appears.

The aromatic diamines, on the contrary, possess a rather strong toxicity, their peculiar action being a destruction of the coloring matter of the blood. According to Dubois and Vignon[4] meta-phenylene-diamine causes vomiting, cough, coma and death. Nevertheless its hydrochloride under the trade name of Lenthin is recommended as an antidiarrheal even for children.[1] There is a still stronger action observed for the para compound, which causes violent inflammations of the internal mucous membranes and cramp paroxyms. The former effect, however, is attributed by Erdmann and Vahlen[2] to quinonediimine,

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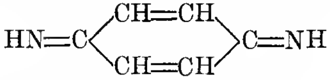
[1] Treupel and Hinsberg, Arch. exp. Path. Pharm., **33**, 216 (1894).

[2] Spiegel and Sahbath, Ber., **34**, 1936 (1901).

[3] Faust, Arch. exp. Path. Pharm., **51**, 262 (1904).

[4] Dubois and Vignon, Compt. rend., **107**, 533 (1888).



which is a first product of oxidation. Quinone imides, according to Brissemoret,[3] also have a purgative effect consequent upon the stimulation of intestinal secretion. The ortho compound has also a remarkably great toxicity.

Toluylenediamines (or diamido toluenes) have a still more powerful action on the blood, producing icterus and hæmaturia.[4]

The blood corpuscles are also peculiarly affected by benzidine, $NH_2—C_6H_4—C_6H_4—NH_2$. In vitro this substance causes the formation of methæmoglobin, although in the organism it is somewhat less active in this direction. In the dog, but not in the rabbit, it causes nausea, vomiting and motor unrest, and in all animals it causes the appearance of considerable sugar in the urine.[5]

An interesting consideration is the influence of hydrogenization upon the physiological activity of the aromatic amines.[6] Thus the two naphthyl-amines produce a paralysis of the central nervous system in animals, the

[1] Boye, Zentr. inn. Med., 1905, 113.

[2] Erdmann and Vahlen, Arch. exp. Path. Pharm., **53**, 401 (1905).

[3] Brissemoret, Soc. biol., **62**, 657 (1907).

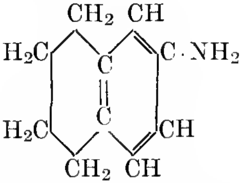
[4] Stadelmann, Arch. exp. Path. Pharm., **14**, 231 (1881); **16**, 118 (1883); **23**, 427 (1887).

[5] Adler, Arch. exp. Path. Pharm., **58**, 167 (1908).

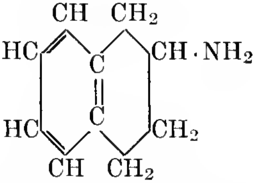
[6] Stern, Virchow's Arch., **115**, 14; **117**, 418 (1889).

α compound acting more strongly than the β compound. The latter body causes also a slight contraction of the pupil of the eye. Of the two tetrahydro-β-naphthylamines,

I



II

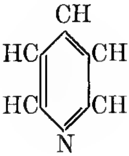


the body (I) which is hydrogenized on the non-substituted ring is inactive, and the other compound (II) which is hydrogenized in the ring which bears the amino group is quite active, causing strong rise in temperature, cramp phenomena, and dilatation of the pupil (mydriasis). The effect of the compound is considerably increased by the introduction of an ethyl group in the amino group, but a methyl group in this position is without appreciable influence.

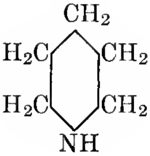
If a second amino group is introduced into the non-hydrogenized ring of the first compound (I), we have the aromatic alicyclic tetrahydro naphthalene diamine, a strongly toxic compound which, however, does not dilate the pupil.

The influence of hydrogenization upon physiological action which we see here, may be also observed in a marked degree in the cyclic bases.

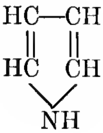
I



II

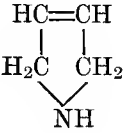


III

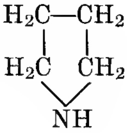


Pyridine (I) shows, to be sure, some effect upon the sensory apparatus, the respiration and heart action; but it may be considered as being comparatively non-poisonous.[1] Piperidine (II), however, has a very essentially stronger action. This acts in warm-blooded animals as a cramp-producing poison, which considerably increases the blood pressure through contraction of the blood vessels, and finally causes paralysis of both central and peripheral nerves. Pyrrole (III) is itself a poison, causing a central nervous paralysis.[2] The greater action of this compound compared with pyridine is probably due to the reactive imino group. But the effect increases in pyrroline (IV) and is still greater in pyrrolidine (V). This latter compound,

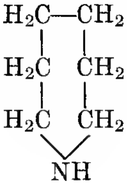
IV



V



VI



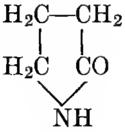
is qualitatively like piperidine, as is also the higher ring homologue cyclohexamethylenamine (VI). Quantitatively, however, the effect is not the same. It increases from pyrrolidine to piperidine to hexamethylenamine. That is, it increases with the size of the ring, as we have already noted in the case of the cyclic ketones. As further example of this general principle, we may also cite the isoximes pyrrolidone (VII), piperidone (VIII), cyclohexanoneisoxime (IX) where the order of activity is the same as the order of the compounds given.

---

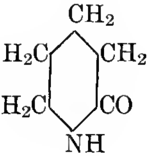
[1] Brunton and Tunicliffe, J. Physiol., **17**, 292.

[2] Ginzberg, Dissertation, Königsberg, 1880; cf. Pighini, Arch. fisiol., **3**, Vol. I (1906).

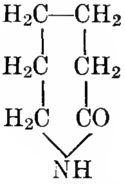
VII



VIII

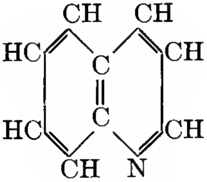


IX

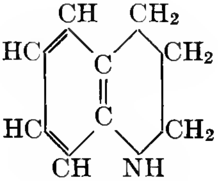


Likewise the toxicity increases from quinoline (X) to tetrahydroquinoline (XI) to decahydroquinoline (XII).[1]

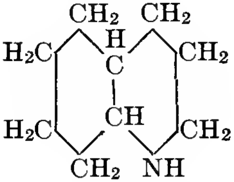
X



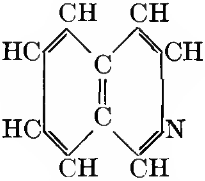
XI



XII



XIII



The same statement holds also in the case of isoquinoline XIII and its hydrogenized bodies as well as with their homologues and derivatives, among which we shall find some of the alkaloids which will receive a special consideration later.

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[1] Heinz, Virchow's Arch., **122**, 116 (1890).

As one further example we may mention that the toxic effect of dihydroindole (Indoline) is greater than that of Indole.[1]

Ammonium Bases

There is a fundamental difference between the compounds of trivalent nitrogen and those of pentavalent nitrogen, in other words between those with free valences and those with saturated valences.[2] In the case of the latter (with pentavalent nitrogen) there is observed quite generally a physiological phenomenon consisting of a paralysis of the motor end-plates.

This action is called the curare effect, from the name of the poison whose administration was observed to be followed by this action. The intensity of this effect diminishes with increasing molecular weight of the compound. It depends also, of course, upon the structure of the compound and the spacial grouping of the radicles combined with the nitrogen.[3]

Accordingly we find in ammonium bases which result from the alkylation of tertiary bases the same special physiological properties which belong to these tertiary bases; but they are very much weakened in the derived bodies. Now then, if this weakening of action takes place upon the undesirable effects more than upon the desirable therapeutic effects, then we can proceed with alkylation. The result is that from alkaloids, for example, which though powerful and effective, are of doubtful value, because of injurious side-effects, we may thus obtain valuable and useful derivatives. A case in point is that of the methyl atropinium salts. Frequently, also, it is a fact that the addition products possess new properties.

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[1] Cuttitta, Bioch. Zentr., **7**, 349 (1908).

[2] C.f. Spiegel, Z. anorg. Chem., **19**, 365 (1902).

[3] Hildebrandt, Arch. exp. Path. Pharm., **53**, 76 (1905).

The curare effect has been observed for the platinum, cobalt, rhodium and chromium ammonia compounds,[1] which argues that in these compounds the ammonia is held, as we have assumed, by means of neutral valences. Furthermore this same effect occurs in the analogues of the ammonium bases, that is in the phosphonium, arsonium and stibonium bases.

We must admit, it is true, that this curare effect is not unconditionally dependent upon the ammonium constitution. To a lesser degree it is also found in some secondary bases (piperidine, coniine, methyl aniline, guanidine)[2] and also in nitrogen-free substances of the camphor group—in fact in camphor itself. The extent to which this effect is favored by the ammonium constitution, however, has been shown by the investigation of Boehm[3] on the curare alkaloids.

He found in this arrow poison, besides the quaternary base Curarine, a tertiary base Curine. Each of these alkaloids is capable of producing the characteristic effect; but the ammonium base Curarine is 226 times as powerful as Curine. This latter alkaloid can be converted by methylation into the former.

Besides the curare effect, there is observed in a series of ammonium bases, another action which was first observed for natural Muscarine (I), and is therefore called the muscarine effect. This consists of the arrest of the heart in diastole in consequence of the excitation of the inhibitory nervous apparatus.

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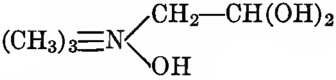
[1] Hofmeister, Arch. exp. Path. Pharm., **16**, 393 (1883) and Bock, ibid., **52**, 1, 30 (1905).

[2] Fühner, Ibid., **50**, 1 (1903).

[3] Boehm, ibid., **35**, 20 (1895), also Arch. Pharm., 235, 660 (1897).

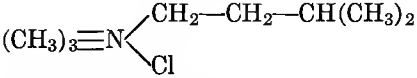
I



$$(CH_3)_3\equiv N\begin{matrix} \diagup CH_2-CH(OH)_2 \\ \diagdown OH \end{matrix}$$

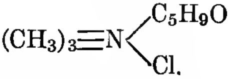
This effect is already exhibited by tetramethyl ammonium chloride and still more by tetramethylammoniumtriiodide[1] further by iso-amyltrimethyl ammonium chloride (II) and by valeryltrimethyl ammonium chloride (III).[2]

II



$$(CH_3)_3\equiv N\begin{matrix} \diagup CH_2-CH_2-CH(CH_3)_2 \\ \diagdown Cl \end{matrix}$$

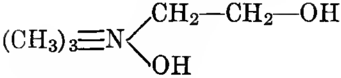
III



$$(CH_3)_3\equiv N\begin{matrix} \diagup C_5H_9O \\ \diagdown Cl. \end{matrix}$$

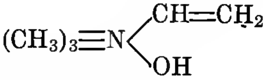
According to Waller and Sowton the effect upon the heart is to be observed in the action of the other bases, which are closely related to Muscarine such as Choline (IV), Neurine (V) and Betaine (VI). Choline and betaine are much less poisonous than Neurine and muscarine.

IV



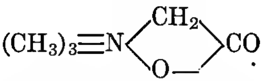
$$(CH_3)_3\equiv N\begin{matrix} \diagup CH_2-CH_2-OH \\ \diagdown OH \end{matrix}$$

V



$$(CH_3)_3\equiv N\begin{matrix} \diagup CH=CH_2 \\ \diagdown OH \end{matrix}$$

VI



It is presumable that stereo conditions in muscarine also have important bearing upon its action, because the choline muscarine obtained by Schmiedeberg from choline by oxidation[1] is physiologically different from the natural muscarine.[2] Both are toxic; but the muscarine from choline causes paralysis of the intermuscular nerve terminations and myosis in the pupils of the eyes of birds, while the natural Muscarine produces neither of these effects. Honda states that the muscarine of toadstools has the same action as the muscarine from choline.[3] Likewise anhydromuscarine (VII), obtained by Berlinerblau[4] and isomuscarine (VIII)[5] differ from muscarine in having no action on the frog's heart or on the pupil of the eye.

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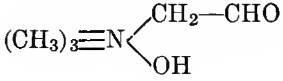
[1] Jacobi and Hagenberg, Arch. exp. Path. Pharm., 48, 48 (1902).

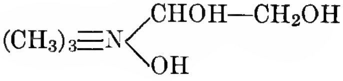
[2] Schmiedeberg and Harnack, Arch. exp. Path. Pharm., 6, 110 (1877).

VII



$$(CH_3)_3{\equiv}N<^{CH_2-CHO}_{OH}$$

VIII



$$(CH_3)_3{\equiv}N<^{CHOH-CH_2OH}_{OH}$$

A lengthening of the side chain in the derivatives of neurine and muscarine diminishes their toxicity. In the same way we find in comparing tetraethylammonium iodide with the tetramethyl compound that the higher homologue possesses the curare effect of the lower body but not its muscarine effect.[6] The corresponding triiodide is lacking in both effects.[7] But in the case of choline, we find that the introduction of the ethyl group into the hydroxyl causes a strong increase in the toxic effect.[1]

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[1] Schmiedeberg and Harnack, Arch. exp. Path. Pharm., **6**, 110 (1877).

[2] Waller and Sowton, Proc. Roy. Soc., **72**, 320 (1903).

[3] Honda, Arch. exp. Path. Pharm., **65**, 444 (1911).

[4] Berlinerblau, Ber., 17, 1139 (1884); E. Fischer, ibid., **26**, 464 (1893); Nothnagel, ibid., **26**, 801 (1893).

[5] H. Meyer s. Schmidt, Ann. Chem., **337**, 37 (1904).

[6] Jordan, Arch. exp. Path. Pharm., 8, 15 (1877).

[7] Jacobi and Hagenberg, l.c.

Cyclic Bases and Alkaloids

Pyridine, as we have already mentioned, has only slight effects upon the sensory nerves or upon the respiration and heart action. It undergoes a special treatment in the organism, due probably to the fact that it does not combine with either glucuronic acid or sulphuric acid after oxidation. It is converted into the methyl ammonium base, $HO \cdot CH_3NC_5H_5$.[2] Its activity is increased by the addition of aliphatic side chains, especially alkyl groups, and its effect upon the sensory nerves particularly is thus augmented.[3] In the series pyridine, picoline, lutidine, collidine and parvoline there is an increasing degree of action which is manifested by an intoxicant effect and an increase in the respiration and pulse frequency.

The same condition holds true for the derivatives of piperidine $C_5H_{11}N$. Piperidine itself causes a strong increase in blood pressure, has a noticeable action on the motor end-plates, that is, an incipient curare effect, and also has an effect upon the heart action. Pipecoline (α-methyl piperidine) has a complete curare effect without arresting the heart action. The same thing is true of α-ethyl piperidine and α-propylpiperidine but in a decreasing degree. But the real toxic effect of the compounds which results in a paralysis of the central nervous system and subsequent paralysis of the motor nerve terminals rises from piperidine to pipecoline to ethyl piperidine to coniine in a geometrical progression 1 : 2 : 4 : 8. If the alkylation is continued very far the ratio is increased. If we replace by successive alkyl radicals the hydrogen of the γ carbon atom in Lupetidine,

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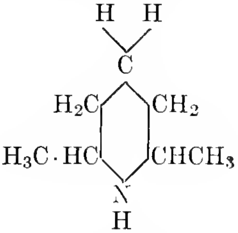
[1] H. Meyer s. Schmidt, l.c.

[2] His, Arch. exp. Path. Pharm., **22**, 253 (1887); Cohn, Z. physiol. Chem., **18**.

[3] Kendrick and Dewar, Proc. Roy. Soc., **22**, 432.



we find that the toxic effect of the resulting compounds increases in a geometric progression for an arithmetic progression of the molecular weight. But this is true only up as far as the propyl derivative. The isobutyl derivative shows a decrease again and the hexyl derivative a still further decrease.[1] Moreover, the position which the radicle occupies upon the nucleus is not without material effect. Thus the lethal dose of β-propyl piperidine is nearly twice as great as that of the α-propyl piperidine (Coniine). But the lethal dose of β-ethyl piperidine is twice as great as that of the α-propyl compound.[2] We should note here, that alkylation on the nitrogen is very important and generally results in an increase in the physiological activity of the compound. This increase, also, is greater than that caused by alkylation on a carbon atom. Here again, there is a rise in the effect up as far as the propyl body and then a decrease in the higher homologues. Considering the compounds where the alkyl radicles are attached to the nitrogen of piperidine we have the following series of lethal doses per kilogram of body weight in the case of a rabbit:

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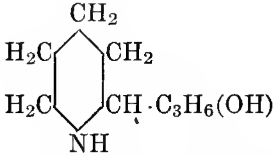
[1] Gürber, Arch. Physiol., 1890, 401.

[2] Ehrlich and Granger, Ber., **30**, 1060 (1897) and Günther, Ber., **31**, 2141 (1898).

N-methyl : ethyl : propyl : amyl as

0.4 : 0.1 : 0.01 : 0.04

Derivatives formed by acylation on the nitrogen cause cramps that can reach a condition of perfect tetanus, as in the case of the formyl derivative.[1] The presence of an hydroxyl group in the side chain seems to weaken the physiological effect of the compound. For an example, Conhydrine,



is qualitatively like coniine, but its action is milder.[2] If the hydroxyl is in the ring, the substances seem to be enabled to act upon the brain; but if such hydroxyls are covered by ether formation the compounds will then further the excitation of cramps.

The derivatives of quinoline have in general a less toxic effect than the corresponding substituted pyridine derivatives. In other words the condensation of a benzol ring with the pyridine weakens its action. On the other hand the inherent antiseptic action of the benzol which we may assume it to have, judging from its oxyderivatives, is considerably increased by this condensation with pyridine.

Let us now take up a discussion of the individual alkaloid groups from the standpoint of constitutional relationships which seem to be responsible for similarities in physiological activities.

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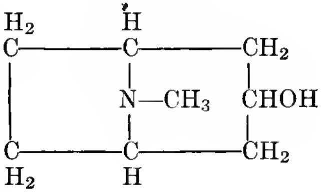
[1] R. and E. Wolffenstein, Ber., **34**, 2408 (1901).

[2] Wertheim, Ann. Chem., **100**, 337 (1856).

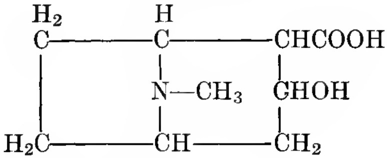
Group of Atropine and Cocaine

These two alkaloids are closely related in chemical constitution. Atropine (III) is derived from tropine (I) and Cocaine (IV) is derived from Ecgonine (II), which is the orthocarboxylic acid of Tropine.

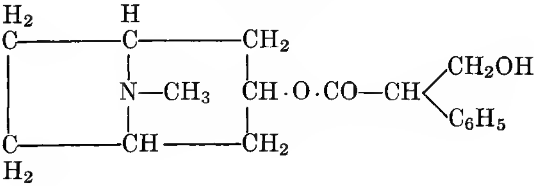
I TROPINE



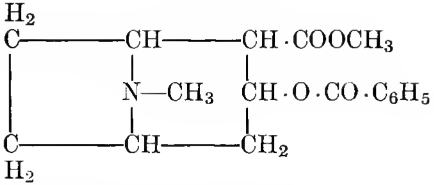
II ECGONINE



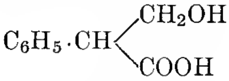
III. ATROPINE



IV. Cocaine



In both of these compounds the alcoholic hydroxyl is esterified by an aromatic acid, tropic acid,



$$C_6H_5\cdot CH\left\langle\begin{array}{l}CH_2OH\\COOH\end{array}\right.$$

in the case of atropine and benzoic acid in the case of cocaine. In the latter, the hydrogen of the carboxyl group of ecgonine is further replaced by the methyl group.

There is a definite physiological relationship which corresponds to this chemical relation. Both alkaloids act in the same way upon the central nervous system, the action being first excitant and then paralyzing. They both have from the start a paralytic effect upon the endings of certain peripheral nerves. But there is one essential difference in this action. While cocaine exercises this effect essentially upon the ends of the sensory nerves (the result being a local anæsthesia) atropine extends its sphere of action to all the organs and nerves upon which muscarine has an excitant effect. These are the inhibitory apparatus of the heart, all glands proper, the motor elements in the organs with plain or unstriped muscle fibers (intestine) and particularly the organs of adaptation and accommodation of the eye.

The pupil of the eye is enlarged (mydriasis) on account of the paralysis of the nervus occulomotorius and consequent lack of nerve control of the ciliary muscle. The result is the impossibility of accommodation for near objects. This effect of atropine is a local one, just like the effect of cocaine upon the sensory nerve ends.

When cocaine is applied to mucous membrane, it causes a pallor due to a contraction of the blood vessels. Other effects that may be mentioned are a foamy degeneration of the liver,[1] a strong rise in temperature,[2] and the property of increasing the capacity for work, which is the reason for the extensive use of cocaine in its native land.[3]

According to some observers[4] atropine has a feeble but appreciable effect on the sensory nerve endings, and cocaine causes a weak but long-continued mydriasis.

Now then, if we are led to believe that the combined ring system which is the foundation of these two alkaloids is the secret of their action upon peripheral nerve ends, we shall at least have to modify our view to include the fact that a suitable substitution in these rings is essential to the action. For tropine has no mydriatic action, but does have an effect upon the heart. Of the tropeines (the organic acid esters of tropine according to Ladenburg) those of the aliphatic acids act essentially like tropine.[5] But when an aromatic acid radicle is introduced, the heart effect becomes more or less obscured, and the nerve effect becomes apparent.[6] In this substitution, however, the character of the acid radicle is the factor which determines whether this effect shall be manifested as mydriatic or anæsthetic. The tropeines of benzoic acid, C_6H_5COOH, of cinnamic acid, $C_6H_5 \cdot CH{=}CH \cdot COOH$, of atropic acid,

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[1] Ehrlich, Deut. med. Wochschr., **17**, 717 (1891).

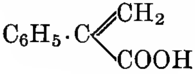
[2] Reichert, Zentr. med. Wissensch., 1889, 444.

[3] Mosso, Pflüger's Arch., **47**, 553 (1890).

[4] Filehne, Berl. klin. Wochschr., **24**, 107 (1887).

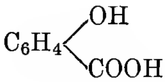
[5] Gottlieb, Arch. exp. Path. Pharm., **37**, 128 (1896).

[6] Buchheim, Arch. exp. Path. Pharm., **5**, 463 (1876).



$$C_6H_5 \cdot C \begin{matrix} {=}CH_2 \\ COOH \end{matrix}$$

and of salicylic acid,



$$C_6H_4 \begin{matrix} OH \\ COOH \end{matrix}$$

cause anæsthesia but no, or only slight, mydriasis. The benzoyl tropeine has a strong anæsthetic action and the benzoic acid ester of pseudotropeine (which is a stereo isomer of tropeine) is the tropacocaine which is found in Java coca leaves. This substance has no mydriatic effect, and is less toxic and a more powerful anæsthetic than cocaine.[1] Only when the tropine is esterified with an organic acid with a side chain which contains an hydroxyl group do we observe the presence of the characteristic atropine effect. For example, as the tropeine of mandelic acid is still nearer to benzoic acid than is tropic acid, so the anæsthetic power of homatropine is stronger than that of atropine. We have already noted that stereo arrangement has a considerable influence in these considerations. According to the investigations of Cushny[2] the optical components of atropine (dextro and lævo hyoscyamine) are each selectively preferred by certain organs, and together they seem to be responsible for the total effect of the racemic isomer. It was found that in mydriatic effect the lævo hyoscyamine is almost twice as effective as atropine and is 12 to 18 times as strong as dextro hyoscyamine.

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[1] Chadbourne, Brit. Med. J., 1892, 402.

[2] Cushny, J. Physiol., Oct., 1903.

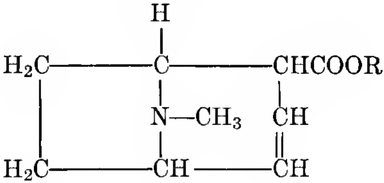
Conversion of atropine into alkyl atropinium salts such as Eumydrin results in an equal but more evanescent mydriatic effect. It also results in a diminution of the other poisonous effects, and is therefore advantageous for therapeutic use.

The atropine action remains practically unchanged when the alcoholic hydroxyl of the tropic acid is replaced by chlorine; but the same substitution by bromine diminishes the effect much more.[1]

Ecgonine has no anæsthetic effect and benzoyl ecgonine and ecgonine methylester show only slight indications of a cocaine effect.[2]

Now one might be led to believe that the effect is dependent upon simply the closing up of both the carboxyl and the hydroxyl groups at the same time. But this is not a tenable theory, for the esters of anhydroecgonine (V) are also without effect.[3]

V. Anhydroecgonine Ester



So we must conclude that this closing up of the carboxyl and alcoholic hydroxyl must be accomplished by certain groups. For the carboxyl, in general any alkyl radicle will suffice. Whether methyl, ethyl, propyl, isopropyl or isobutyl is used the effect is the same.[1] In the case of the hydroxyl group, however, the benzoyl radicle seems to be rather essential and unique in its influence. With all other acids, the esters obtained have at most only a weak anæsthetic effect.[2] The mandelic acid ester is essentially mydriatic like that of tropine. Therefore we may say that alkylation removes the disturbing influence of the carboxyl group when it is on the carbon atom next to the benzoylated hydroxyl group; but it does not do so when it takes place on the same carbon atom that carries the hydroxyl. For example, α-ecgonine (VII) was prepared by Willstätter[3] from tropinone (VI).

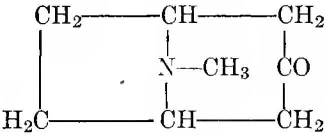
---

[1] Lewin and Guillery, Die Wirkungen von Arzneimitteln und Giften auf das Auge, Berlin, 1905, p. 204 ff.

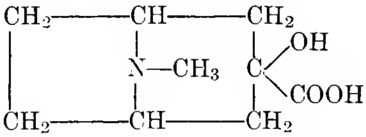
[2] Stockmann, Pharm. J. Trans., **16**, 897 (1888).

[3] Einhorn and Konek de Norwall, Ann. Chem., **280**, 96 (1894).

VI. Tropinone



VII. α-Ecgonine



Now if the carboxyl of this compound is methylated and the hydroxyl is benzoylated the resulting compound has no anæsthetic effect. But we shall see that when the nucleus has a somewhat different structure this combination may also be active.

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[1] Falck s. Merck, Ber., **18**, 2955 (1885); Novy, Am. Chem. J., **10**, 147 (1888).

[2] Liebrich and Liebermann, Ber., **21**, 2344 (1888); Ehrlich, Deut. med. Wochschr., **17**, 717 (1891).

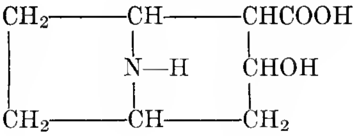
[3] Willstätter, Ber., **29**, 2216 (1896).

Dextro cocaine has a more intense but more evanescent action than the natural lævorotary base.[1]

The methyl group of the nitrogen bridge seems to be without significance for the anæsthetic action, since Norcocaine (the methyl ester of benzoyl Norecgonine, (VIII) possesses this action to the same degree as cocaine but has a stronger toxic effect.[2]

NORCOCAINE

VIII



A further attachment of methyl iodide causes a loss of the anæsthetic effect. The effect upon the liver which is constantly observed in the cocaine derivatives is also absent.[3]

The same result is accomplished if an amino group is introduced in the meta position in the benzoyl group of cocaine. Also, the benzol-sulpho derivatives of this amine and of the urea are without effect upon the liver. But as soon as the amino group is substituted by acid radicles the liver effect is again observed. The acetyl-amino and benzoylamino cocaine possess no anæsthetic effect; but the corresponding urethane has a greater action in this respect than cocaine itself. Considering for a moment the effect of the other substitutions in the cocaine molecule we find that halogen and nitro groups decrease the anæsthetic action without altering the liver effect.

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[1] Poullson, Arch. exp. Path. Pharm., **27**, 301 (1890); Ehrlich, loc. cit.

[2] Poullson, loc. cit.

[3] Ehrlich, loc. cit.

The oxy-cocaines are intermediate in physiological action between the nitro and the amino compounds. The hydrochloride of dextro-cocaine azodimethylaniline causes at most faint traces of anæsthesia, while the hydrochloride of dextro cocaine-azo-α-naphthylamine causes a distinct even if only slight anæsthesia. Neither of these compounds have the characteristic liver effect.[1]

We may say, then, that there is a special significance in the benzoyl group. As this was also observed in a whole series of benzoyl derivatives of other alkaloids, Filehne [2] was led to consider this group as directly responsible for the anæsthesia action. But we have seen instances where this action is entirely lacking either in consequence of a disturbing group (as the carboxyl group in benzoyl ecgonine) or in consequence of an unfavorable structure, even though that structure differs only slightly from that of cocaine (as in the methyl ester of benzoyl norecgonine). Further experiences show that although the benzoyl group favors this anæsthetic activity, it is not absolutely essential.[3] We may say then, that the benzoyl group in itself is not directly responsible for this action; but that rather the effect is brought about by a structure of the nucleus which makes the power of the benzoyl group available. A comparison with the substances which are mydriatically active forces us to believe that the capacity for paralyzing the peripheral nerve endings is inherent in the nitrogen-containing nucleus, and that the acid radicle acts, we may say as a selective anchor which attaches the action to definite nerve endings. Thus, in the case of the benzoyl group, the sensory nerves are the seat of the attachment. In other words, in this specific case, the benzoyl group will furnish the hold upon the nerves, and whether anæsthesia will result or not, must depend upon the nitrogen-bearing nucleus that is attached to the benzoyl group.

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[1] Ehrlich and Einhorn, Ber., 27, 1870 (1894).

[2] Filehne, Berl. klin. Wochschr., 24, 107 (1887).

[3] Ehrlich and Einhorn, loc. cit.

The fact that the benzoyl group seems to have this selective action is responsible for the interest that was aroused in the benzoyl derivatives whose structure is somewhat near that of tropine. These compounds were experimented upon to the neglect of other derivatives of ecgonine and tropine. Two bodies which received such attention are triacetone alkamine and vinyl-diacetone alkamine. Two derivatives of these substances have proved to have an anæsthetic action very similar to that of cocaine. These are Eucaine (benzoyl triacetone alkamine carboxylic acid methyl ester) (I) and Eucaine B (benzoyl vinyl diacetone alkamine or 2-6-6 trimethyl 4-benzoxypiperidine) (II). In this case, as in the cocaine series, it appears that the elimination of the methylated carboxyl group is of little importance. That the removal of the methyl group attached to the nitrogen does not impair the effect is most certainly established by the fact that the norcocaines are as active as the cocaines. Other relationships between the two series were established by Vinci.[1] Among other points it was found that in this case also only one of the stereometric isomers is active.

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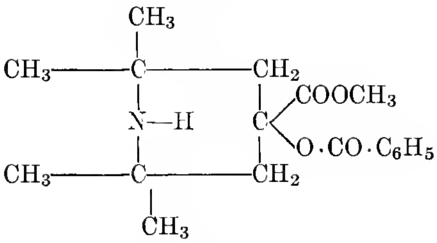
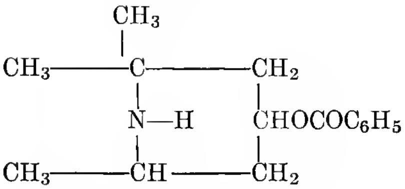
[1] Vinci, Virchow's Arch., **145**, 78 (1896); **149**, 217 (1897); **154**, 549 (1898).

I. Eucaine



II. Eucaine (B)



The work of Einhorn and Heinz[1] resulted in a great simplification in the complex to be benzoylated. For they discovered that it was not necessary, as formerly supposed, and as in the case in the cocaines, that the nitrogen atom shall belong to a ring system.

In fact they found that nearly all amino-oxy-benzoic acid esters have a local anæsthetic action. Representatives of this group are Orthoform (I), which is the methyl ester of para-amino-meta-oxybenzoic acid, and Orthoform new (II), which is meta-amino-para-oxybenzoic acid methyl ester. These compounds are difficultly soluble powders and are useful only for reacting on exposed nerve ends. Such a use is found in cases of burns. The soluble salts react too strongly acid and consequently cause an excessive irritation of the tissues. It was expected that this disadvantage could be overcome by using glycocoll derivatives. Nirvanin (III), for example, is the methyl ester of di-ethyl-amino-acetyl-para-amino-ortho-oxy-benzoic acid, and this substance has found practical application.[1]

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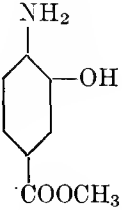
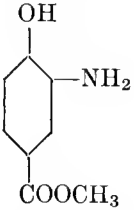
[1] Einhorn and Heinz, Münch. med. Wochschr., 44, 931 (1897).

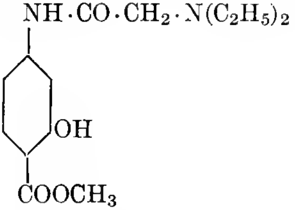
I. Orthoform



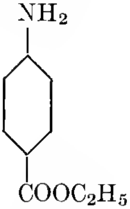
II. Orthoform New



III. Nirvanin



IV. Anæsthesin



It was afterwards determined, however, that the hydroxyl group is not a necessary requisite for the anæsthetic action of such compounds. Rissert recommended the use of the ethyl ester of para-amino-benzoic acid (IV), which was marketed under the name Anæsthesin.[2] A more recent member of this group is Cycloform, which is the isobutyl ester of para-amino-benzoic acid, $NH_2—C_6H_4—COOC_4H_9$, investigated by Impens.[3]

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[1] Einhorn and Heinz, Münch. med. Wochschr., **45**, 1554 (1898).

[2] Pharm. Ztg., **47**, 356 (1902).

[3] Therap. Gegenw., 51, 348.

This investigator states that the amyl and the benzoyl esters have an even greater effect. This is a good example of increase of action with increase of carbon content of the esterifying alkyl group.

The trouble with these last-named compounds, however, is their slight solubility, which renders their practical application as analgesics very slight. Even cycloform is rather difficultly soluble in water, being only .014 to .022 per cent at 10° to 22° C. But these solutions have an action about as strong as saturated solutions of the propyl or ethyl esters, although these contain .03 to .04 per cent and .08 per cent respectively. We may in fact find an advantage in cycloform over the lower homologues in that its solubility results in a correspondingly lower resorption capacity. This is an advantage because the amino-benzoic acids, just like aniline, cause methæmoglobinuria. These compounds in contradistinction to the amino-oxy benzoic acid esters, do not in vitro convert the blood-coloring matter to methæmoglobin. These amino-benzoic acid esters are, as a consequence of their slight solubility, used almost exclusively externally. Subcutine [1] is a similar body and is capable of sterilization without decomposition; but has not met with a very favorable reception. This is a para-phenolsulphonic acid salt. The propyl ester of this compound is better still, and is used under the name of Propæsine.[2]

We must remark, however, that none of these compounds containing the nitrogen atom on the benzol ring has been generally recognized as a wholly satisfactory substitute for cocaine. Besides other special disadvantages they seem to lack the power of deep penetration which that substance has. Much better results were obtained when the position of the nitrogen atom was shifted to the alcoholic group. A series of such compounds which possessed a strong anæsthetic effect, was prepared by Fourneau.[1] Of this series the member which has proved to be most useful in practice is Stovaine. This is the benzoic acid ester of di-methyl-amino-dimethyl-ethyl-carbinol (V). The Farbenfabriken vorm. Friedr. Bayer u. Co. prepared and introduced another compound which they called Alypin (VI) by the introduction of a dimethyl-amino group on the second methyl group of stovaine.[2]

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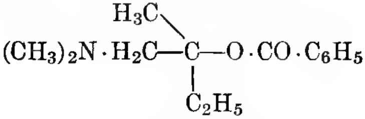
[1] Pharm. Ztg., 48, 405 (1903).

[2] Stürmer and Luders, Deut. med. Wochschr., 34, 2310 (1908).

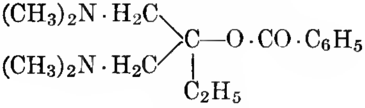
This naturally acts very much like stovaine; but it has the advantage that its salts have a neutral reaction. A third body in this group was introduced by the Farbwerke Meister, Lucius u. Bruening, Höchst a. Main, under the name of Novocaine. This is a diethyl-amino derivative of their anæsthesin, and consequently is para-amino-benzoic acid diethyl-amino-ethyl ester or para-amino-benzoyl-diethyl-amino ethanol (VII).[3]

V. Stovaine



$$(CH_3)_2N\cdot H_2C-\overset{\displaystyle H_3C}{\underset{\displaystyle C_2H_5}{C}}-O\cdot CO\cdot C_6H_5$$

VI. Alypine



$$\left.\begin{array}{l}(CH_3)_2N\cdot H_2C\\(CH_3)_2N\cdot H_2C\end{array}\right>\underset{\displaystyle C_2H_5}{C}-O\cdot CO\cdot C_6H_5$$

VII. Novocaine

$$(C_2H_5)_2N\cdot CH_2\cdot CH_2-O\cdot COC_6H_4-NH_2$$

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[1] Fourneau, Compt. rend., **138**, 766 (1904).

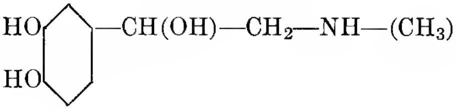
[2] Impens, Deut. med. Wochschr., **31**, 1154 (1905).

[3] Braun, Deut. med. Wochschr., **31**, 1667 (1905).

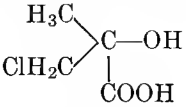
Although the investigations upon these three substances, particularly on their comparative value, cannot be said to be concluded, nevertheless we can say that they all stand very near cocaine and the eucaines as far as the manner of their anæsthetic action is concerned, and moreover they have the advantage of being less toxic. On the other hand they lack one of the advantages of cocaine, which is often desirable, and that is the power of contracting the blood vessels. In fact stovaine and alypine have the opposite effect, causing a dilation of the blood vessels.

This brings us to a substance which comes to the rescue in this condition, a substance which is also related in constitution and has in itself a slight anæsthetic action, although its pre-eminent powerful effect is vasocontractile. This substance is Adrenaline.[1]

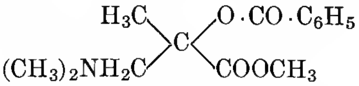
Adrenaline



According to Fourneau[2] the simplest analogue of cocaine is obtained from chloroxyisobutyric acid,



and has the formula



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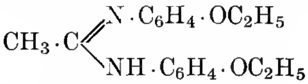
[1] Zeigan, Therap. Monatsh., April, 1904.

[2] Fourneau, J. pharm. chim., (6) 27, 513 (1908).

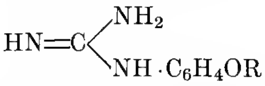
It differs from stovaine by having a carboxyl group instead of an ethyl group. As a matter of fact it is really more comparable with methyl-benzoyl-α-ecgonine than with cocaine. Nevertheless it possesses a strong anæsthetic power (compare also eucaine). It cannot be used in practice because the fundamental basic character of the substance is so weak that its salts have an acid reaction. Fourneau also says that for a practically useful cocaine substitute the compound must have at least two carbon atoms between the two ester groups.

A very decided anæsthetic effect is shown by the alkaloid Yohimbine [1] although it contains no benzoyl group. Yohimbine does not have a mydriatic action, but does dilate the blood vessels. An anæsthetic effect is found, also, in the glucosides of the digitalis group. These substances cause at the same time a contraction of the pupil and more or less hyperæmia.[2] Anilides have to a slight degree an anæsthetic action as also have the ordinary phenetidine derivatives. The action is, however, increased, by the addition of a second basic complex to the amino group, as for example in Holocaine, which is para-diethoxy-diphenyl-ethanyl-amidine,[3]



$$\mathrm{CH_3\cdot C}\begin{array}{l}\diagup\!\!\diagup\,\mathrm{N\cdot C_6H_4\cdot OC_2H_5}\\ \diagdown\,\mathrm{NH\cdot C_6H_4\cdot OC_2H_5}\end{array}$$

or in the alkyl-oxyphenyl guanidines,[4]



$$\mathrm{HN{=}C}\begin{array}{l}\diagup\,\mathrm{NH_2}\\ \diagdown\,\mathrm{NH\cdot C_6H_4OR}\end{array}$$

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[1] Arnold and Behrens, Chem. Ztg., **25**, 1083 (1901). Magnani, Münch. med. Wochschr., **50**, No. 28 (1903); Loewy and Müller, Münch. med. Wochschr., **50**, No. 15 (1903).

[2] Korizki, Dissertation, Petersburg, 1906.

[3] Täuber, Therap. Monatsh., April, 1897.

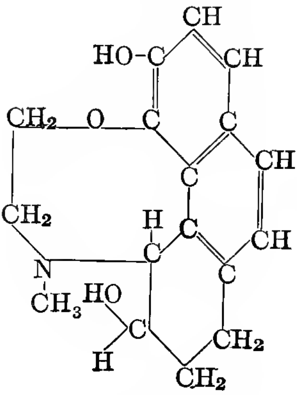
[4] Trolldenier, Therap. Monatsh., 1899, 36.

Finally we may mention that this anæsthetic action is also found in phenols and phenol ethers with at least one free hydroxyl, in α-aminopyridine, tri-methylethylene, etc.[1]

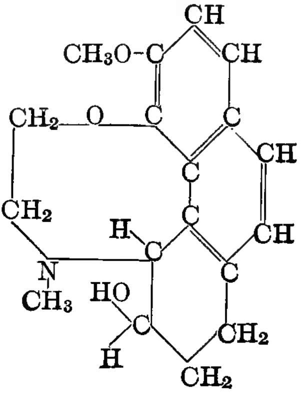
Opium Alkaloids and Relatives.

The most important substance in opium is morphine (I). This is a phenanthrene derivative, as are also codeine (II) and thebaine (III).

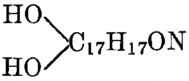
I. Morphine



II. Codeine

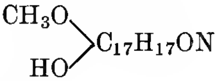


I. Morphine



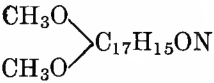
$$\left.\begin{matrix}HO\\HO\end{matrix}\right> C_{17}H_{17}ON$$

II. Codeine



$$\left.\begin{matrix}CH_3O\\HO\end{matrix}\right> C_{17}H_{17}ON$$

III. Thebaine



$$\left.\begin{matrix}CH_3O\\CH_3O\end{matrix}\right> C_{17}H_{15}ON$$

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[1] Fränkel, Arzneimittelsynthese, 2d Ed., p. 380.

Morphine and of course codeine, which is methyl morphine, are derived from hexahydrophenanthrene, while thebaine is derived from tetrahydrophenanthrene. The physiological effect of morphine is somewhat complicated. In the first place it diminishes and finally stops the functioning of the cerebrum, particularly the power of sensation. This is the cause of the most potent and important results of the administration of morphine, which are a deadening of pain, hypnosis, euphoria and narcosis. After larger doses the paralysis extends to the voluntary movements and to the reflex movements which depend upon pain production for excitation and which are also finally completely suppressed. In some kinds of animals morphine acts like strychnine in causing an increase in the sensitiveness of reflex actions, which are controlled by sense excitation. This effect is much more pronounced in the case of codeine, and is entirely preeminent in thebaine, which should be placed, as far as physiological action is concerned, in the strychnine group.

Morphine is attracted to the brain and is here largely destroyed. The extent of the attraction and destruction by the brain substance is, moreover, commensurate with the habituation or tolerance which results from continued use.[1]

First of all, it is of interest to investigate the extent of the rôle of the phenanthrene nucleus in this effect. It is true that Overton has stated that phenanthrene itself acts as a narcotic on tadpoles; but with warm-blooded animals it has no such action. On the other hand, it undoubtedly does have a tetanic effect. This is also true of the phenanthrols, the carboxylic acid, and even of the sulphoacid. 4-methoxy-phenanthrene-9-carboxylic acid acts like phenanthrene carboxylic acid. A further addition of alkyl and acid groups upon the hydroxyl diminishes very considerably the cramp producing action and the general toxic effect. None of these preparations, however, possesses any narcotic action.[1]

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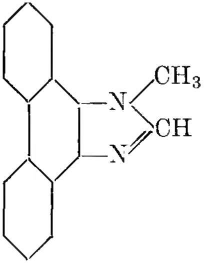
[1] Cloetta, Arch. exp. Path. Pharm., **50**, 453 (1903).

The action of phenanthrene quinone derivatives, is somewhat different. Phenanthrene quinone-3-sulphonic acid has no cramp effect, but does cause pronounced methæmoglobinuria,[2] 2-brom-phenanthrene quinone sulpho acid causes strong poison phenomena and degeneration of the organs, and is said to act, when introduced directly into the veins, in a manner similar to morphine, in so far as it retards and diminishes the respiration.[3] According to Pschorr[4] we must also consider as belonging here the Epiosin of Vahlen[5] which is methyl-diphenylene-imidazol (IV). This substance dulls the sensibility for pain, has a slight hypnotic effect, and a strong cramp, producing action. Like Schmidt's compound, it causes an increase in blood pressure.

IV. Epiosin



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[1] Bergell and Pschorr, Z. physiol. Chem., **38**, 17 (1903).

[2] Ibid.

[3] Schmidt, Ber., **37**, 3565 (1904).

[4] Pschorr, Ber., **35**, 2729 (1902).

[5] Arch. exp. Path. Pharm., **47**, 368 (1902).

According to Pschorr the morphine-like effects are not caused by action upon the nerves, as in the case of morphine itself, but by a poisoning of the blood.

Therefore it seems as if the narcotic effects of morphine were dependent upon the addition of a nitrogen-containing ring. In order to cause a stronger action the phenolic hydroxyl of the morphine must be free, for it is evident that this group functions as a binder of the alkaloid to the nerve substance. To be sure, codeine, in which this hydroxyl is methylated, does produce in small doses a narcotic effect, but it is of much shorter duration and less deep than that of morphine. Upon the administration of larger doses of codeine, this narcosis is hardly perceptible, because the tetanic effect becomes of paramount importance.[1]

The same is true of the action of ethyl morphine (Dionine), amyl morphine and benzyl morphine (Peronine). Similar changes in effect are caused by the introduction of acid radicles such as acetyl, benzoyl, etc., into the phenolic hydroxyl.[2] Such compounds, however, stand nearer to morphine than do codeine and its homologues, because in the former compounds the radicles which hinder or retard the morphine effect are more easily split off. Diacetyl morphine (Heroine) finds a considerable practical application. The inorganic acid radicles act in a manner similar to the organic acid radicles. The more easily the acid radicle can be split off, the more nearly the effect approaches that of morphine. For example, the carbonic esters and the carbonic acid alkyl esters of morphine act very much like morphine, according to von Mering. Winternitz[3] states that alkylation of morphine weakens the effect upon the respiration, but acylation strengthens it very materially.

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[1] Stockmann and Dott, Brit. Med. J., 1890, II, 189.

[2] Ibid.; v. Mering, Merck's Jahresber., 1898, 5.

[3] Winternitz, Therap. Monatsh., Sept., 1899.

These derivatives of morphine furnish remarkable examples of the fact that it is exceedingly dangerous and uncertain to assume that a chemical compound will have the same effect upon man that has been observed with other warm-blooded animals. For example, codeine is much more poisonous for rabbits than is morphine. For man, on the contrary, codeine is much less poisonous.[1] For experiments which affect the nervous system it appears that the cat is most suitable if the results are to be compared to those in man.

Of the products which result from tearing down the morphine molecule, apomorphine is only a mild narcotic, but it has a powerful emetic action, which is to be attributed to the free phenolic hydroxyls. The reason for attributing it to these groups is that a half alkylation leaves only a suggestion of the emetic action, and complete alkylation or acylation removes it entirely.[2]

On the other hand this specific emetic effect is not destroyed by conversion into quaternary compounds. For example, the effect is retained in apomorphine brommethylate (Euporphine), but the undesirable side effects, such as action upon the heart, are said to be eliminated.[3]

The methylated derivative, apocodeine, acts as a sedative and purgative.[4] Dixon [5] states that it has a paralytic action upon the nerve cells, thus causing dilation of the blood vessels, that it depresses the blood pressure, accelerates the heart frequency, and excites the automatic movements of the smooth muscles. Moreover, it increases the reflex action even to convulsions, like those caused by strychnine, and finally it has a curare effect.

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[1] Mayor, Therap. Monatsh., May–June, 1903; Vinci, Arch. ital. di Biol., **47**, Vol. III (1907).

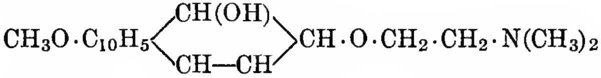
[2] Michaelis, Klin.-therap. Wochschr., 1904, 660; Kaminer, Festschr. f. Salkowski, p. 205.

[3] Schütze, Berl. klin. Wochschr., **43**, 349 (1906).

[4] Guinard, Contribution à l'étude physiologique de l'apocodeine, Lyon, 1893. Toy and Combemale, Merck's Jahresber., 1900, 62.

[5] Dixon, J. Physiol., **30**, 98 (1904).

The methyl-morphimethines

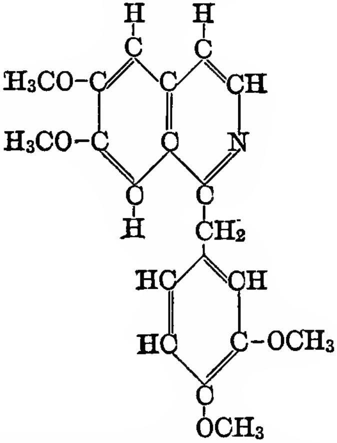


$$CH_3O\cdot C_{10}H_5\left\langle\begin{array}{c}CH(OH)\\ CH{-}CH\end{array}\right\rangle CH\cdot O\cdot CH_2\cdot CH_2\cdot N(CH_3)_2$$

act neither as relievers of pain, nor as sleep producers. They do, however, like morphine, paralyze the respiratory center, and unlike it lower the blood pressure.

Intermediate in effect between morphine and codeine stands papaverine (I) [1]

I. Papaverine



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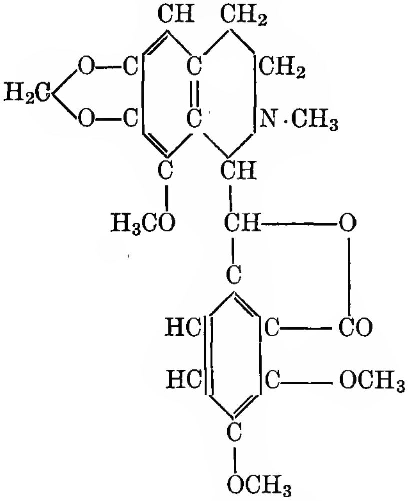
[1] Schroeder, Arch. exp. Path. Pharm., 17, 96; Leubuscher, Deut. med. Wochschr., 18, 179 (1902).

Laudanosine, which is the tetrahydro derivative of papaverine, but is methylated on the nitrogen[1] has no appreciable narcotic effect, and is in both its action and toxicity similar to thebaine.[2]

Narcotine (II) is nearer to morphine both chemically and physiologically. It has, however, a much weaker narcotic effect, which is preceded by a tetanic effect of short duration. Hydrastine (III) is very closely related chemically to narcotine; but it has no narcotic effect, and we must attribute this lack to the presence of a methoxyl group. Hydrastine has a toxic effect which is manifested by general paralysis and tetanus.

II. NARCOTINE



The strychnine-like excitant action of hydrastine upon the central nervous system is manifested first through the

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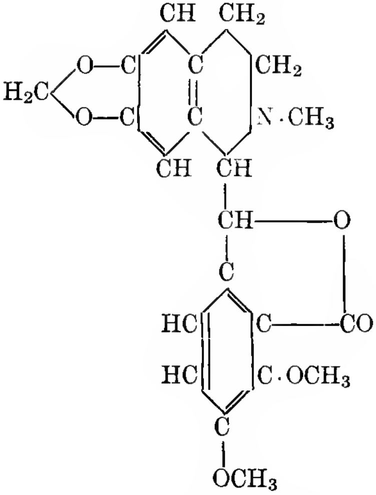
[1] Pictet and Athanasescu, Ber., **33**, 2346 (1900).

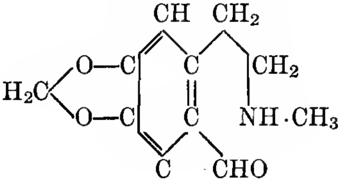
[2] Babel, Rev. méd. de la Suisse rom., 1899, 657.

III. HYDRASTINE



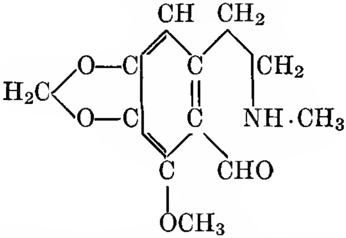
vasomotor nerves, so that small doses cause a contraction of the blood vessels and thus an increase in blood pressure. Considering for a moment the action of some of the decomposition products of these two alkaloids, we find that opianic acid is narcotic through a paralysis of the central nervous system in cold-blooded animals, but in warm-blooded animals it is without effect. Hydrastinine (IV) is distinguished from the parent body by an absence of the tetanic stage and by a detrimental effect upon the heart.

IV. HYDRASTININE



It causes vaso-constriction and thereby a rise in blood pressure, and a lowering of the pulse frequency by action upon the vessels themselves. Cotarnine (V) has been known longer, and its chemical similarity to hydrastinine induced the belief that it also, like hydrastinine, might possess astringent and styptic properties.

V. Cotarnine



The hydrochloride (Stypticine) and later the phthalic acid salt (Styptol) were in fact found to have a styptic action. But, strange to say, the cause of this action was quite different from the cause of the similar action of hydrastinine salts. For the stypticine and styptol cause neither a vaso-contraction nor blood coagulation.[1] Their styptic effect probably depends upon a slowing of the respiration and consequent reduction of arterial blood pressure. The action of cotarnine is similar to that of the parent substance, narcotine. It causes first an excitation of the central nervous system, and then a general paralysis.[2] It is claimed by Williams[3] that an intravenous injection of hydrastis causes a lowering of the blood pressure by a reduction of the action of the heart muscles.

Hydrocotarnine has the typical effect of the codeine group.[4]

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[1] Marfori, Arch. ital. di Biol., 1897, Vol. II.

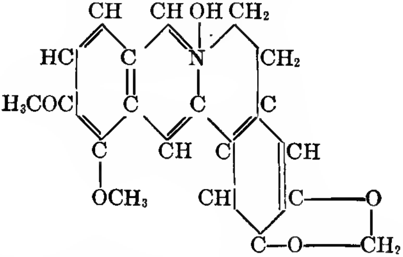
[2] Falk, Therap. Monatsh., 1895, 646 and 1896, 28.

[3] Williams, J. Am. med. assoc., **50**, 26 (1908).

[4] Stockmann and Dott, Brit. med. J., 1891, 24 Jan.

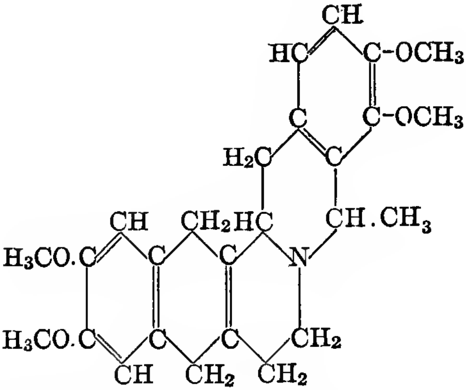
Berberine (I) acts like hydrastine, but is more powerful.[1]

(I) BERBERINE.



The corydalis alkaloids, with the exception of the very weakly basic corytuberine, produce in cold-blooded animals a morphine-like narcosis. These alkaloids stand very near, chemically, to those we have just been discussing, as will be seen from the structural formula proposed for corydaline (II) by Dobbie and Lauder.[2]

II. CORYDALINE



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[1] Williams, loc. cit.

[2] Dobbie and Lauder, Journ. Chem. Soc., 81, 145, 157 (1901).

These corydalis alkaloids can be chemically and also pharmacologically divided into three groups: First, the corydaline group (corydaline, corybulbine, isocorybulbine); second, the corycavine group (corycavine and corycavamine); third, the bulbocapnine group (bulbocapnine, corydine and corytuberine). Common to all three groups is a narcotic effect, an action on the heart, consisting of a weakening of its general capacity for reaction and injury to the muscle motor apparatus. Besides these common effects the alkaloids of the first group cause paralysis of the spinal cord, the second stimulate the motor centers and the third group resemble codeine in action and cause increased reflex excitability.[1]

Veronal Group

The investigations of E. Fischer and v. Mering on dialkylated acids and their derivatives[2] are very instructive concerning the influence of an accumulation of alkyl groups upon a compound, the effect of the size of the radicle and the effect of the constitution of the ring in the production of narcotic effect. We produce, therefore, an exhaustive table of experiments which were made upon dogs. From this table one can observe that there is no sleep-producing effect until we come to the urea group, and it is decidedly stronger in a cyclical arrangement of this group. Furthermore, it is essential that there be in the combination a group that contains several alkyl radicles rich in carbon.

These alkyl radicles cause an increase in effect with rising carbon content of the radicle up as far as propyl, and after that the effect again diminishes. A very strik-

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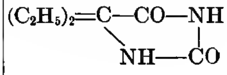
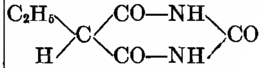
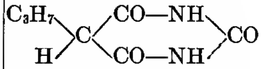
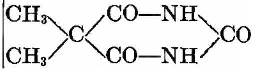
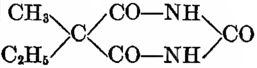
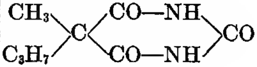
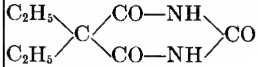
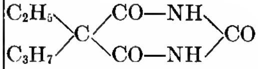
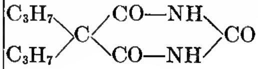
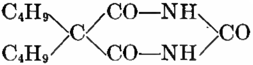
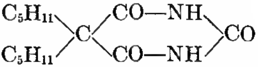
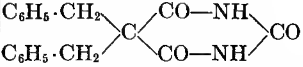
[1] Peters, Arch. exp. Pathol. u. Pharmakol., **51**, 130 (1904).

[2] Therapie der Gegenwart, **5**, 97 (1903).

Compound.	Constitution.	Weight of animal, kg.	Dose.	Action.
A. Acids				
1. Diethylacetic acid	$(C_2H_5)_2{=}CH\cdot COOH$	7.5	5 gms. per os	No action.
2. Diethylmalonic acid	$(C_2H_5)_2{=}C{=}(COOH)_2$			
3. Diethyloxalic acid	$(C_2H_5)_2{=}C(OH)\cdot COOH$			
4. Dimethyl-ethyl-acetic acid	$(CH_3)_2{=}C(C_2H_5)\cdot COOH$			
B. Amides				
5. Diethylacetamide	$(C_2H_5)_2{=}CH\cdot CO\cdot NH_2$	7.5	4–5 gms.	No action.
6. Diethylmalonamide	$(C_2H_5)_2{=}C{=}(CO\cdot NH_2)_2$			
7. Dipropylmalonamide	$(C_3H_7)_2{=}C{=}(CO\cdot NH_2)_2$			
8. Trimethylacetamide	$(CH_3)_3{\equiv}C{-}CO\cdot NH_2$			
C. Urea Derivatives.				
9. Diethylacetylurea	$(C_2H_5)_2{=}CH\cdot CO\cdot NH\cdot CO\cdot NH_2$	8	2 gms.	Phenomena of intoxication.
		5.5	3 gms.	Sleep after 1 hour, long continued after effect—dizziness.
		5	1 gm.	No apparent effect.
10. Dipropylacetylurea	$(C_3H_7)_2{=}CH\cdot CO\cdot NH\cdot CO\cdot NH_2$	5	1 gm.	For several hours, uncertainty, vagueness and drowsiness.
11. Diethylhydantoin		7.5	1.5 gms.	No visible effect.
			2.5 gms.	Slight vagueness and heaviness.

Compound.	Constitution.	Weight of animal, kg.	Dose.	Action.
12. Monoethylmalonylurea		6	3–4 gms.	No appreciable effect.
13. Monopropylmalonylurea.				
14. Dimethylmalonylurea		6	3 gms.	No action.
15. Methylethylmalonylurea		7.5	1 gm. 3 gms.	No effect. After 1 hr. deep sleep, lasting the whole day. On the afternoon of the following day there was still great uncertainty of movement.
16. Methylpropylmalonylurea.		7.5	1 gm.	Transient drowsiness.

Compound.	Constitution.	Weight of animal, kg.	Dose.	Action.
17. Diethylmalonylurea (Veronal)		7.5	1 gm. .5 gms.	Sleep after a little over 1 hour. After 30 minutes a deep sleep lasting over 24 hours.
18. Ethylpropylmalonylurea		8	1 gm.	After 1 hour a deep sleep lasting 24 hours
19. Dipropylmalonylurea (Propanal)		7.5	1 gm.	After 30 minutes deep sleep lasting over 48 hours.
		8	2 gms.	After 15 minutes death-like sleep, next morning dead.*
20. Diisobutylmalonylurea.		7.5	1 gm.	After 30 minutes heavy intoxication, then 8 hours' sleep.
21. Diisoamylmalonylurea.		7.5	1 gm. +2 gms.	After 2 hrs. no effect. Dizziness, no sleeep.
22. Dibenzylmalonylurea		7.5	3 gms.	No apparent effect.

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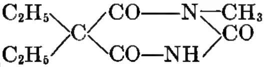
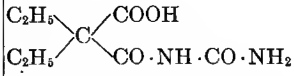
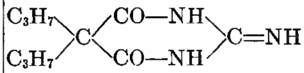
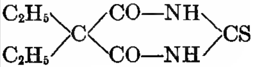
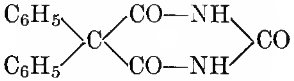
* The strong toxic effect is not observed in the pure propanol. Fischer and v. Mering, Med. Klinik, 1905, 1317; Wunderer, Wien. med. Pr., **47**, 1197 (1906); Möschen, Münch. med. Wochenschr., **53**, 744 (1906).

Compound.	Constitution.	Weight of animal, kg.	Dose.	Action.
23. Diethyl-N-methyl-malonylurea.		6	1 gm.	After 10 minutes, heavy intoxication; after 20 minutes deep sleep lasting 2 days; then death. During the sleep slight twitchings.
24. Diethylmalonic acid ureide.		7	3 gms.	No effect.
25. Dipropylmalonyl-guanidine.				
26. Diethylmalonylthio-urea.		7	1 gm.	After 1 hour deep sleep. After 8 hours death.

ing phenomenon is the increase in toxicity upon methylation on the nitrogen (23) and upon the introduction of sulphur in place of oxygen (26). Contrary to this is the replacement of the same oxygen by NH (25) which nullifies the action. It is easier to understand removal of the effect caused by a free carboxyl group (24 as compared with 9). It would be interesting to determine whether esterification of this group would reestablish the effect.

A slight chemical modification of Veronal which has given rather surprising physiological results is the so-called Luminal of the Farbenfabriken of Elberfeld. One of the ethyl groups of veronal is replaced by phenyl, giving phenyl-ethyl-barbituric acid:



$$\begin{array}{l} C_6H_5 \\ C_6H_5 \end{array} > C < \begin{array}{l} CO-NH \\ CO-NH \end{array} > CO$$

Although in general the aliphatic radicles are more effective in sleep-producing action than aromatic radicles, the reverse seems to be true in this case since, 0.2 gm. of Luminal is equivalent to 0.5 gm. of Veronal. According to Impens, however, this hypnotic action of the aromatic radicle can take effect only when there is attached to the same carbon atom with it one or two other alkyl groups.

Quinine and Fever Remedies Deduced from Quinine

According to Schmiedeberg[1] the general character of the physiological action of quinine is probably to be interpreted as being a sort of mortification effect for all the organs concerned. The functions or the functional capacity of the organs, and their nutrition processes are at first increased, then lowered, and finally entirely destroyed, as in the case of mortification from other causes.

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[1] Schmiedeberg, Grundriss der Pharmakologie, 1902, p. 179.

A .5 per cent to 1 per cent solution of quinine immediately suppresses the movements of all kinds of infusoria. A solution of this concentration also stops the amœboid movements of the white blood corpuscles of mammals.

For man and other mammals small doses lessen the pulse frequency and increase the blood pressure, while larger doses (upward from 1 gm. in the case of man) cause a decrease in pulse frequency and also a decrease in blood pressure. At the same time there appears a weak morphine effect on the sensory brain sphere, which is called quinine intoxication. Smaller doses cause also at first a rise in the body temperature; but larger doses, not sufficient for poisoning effect, of course, have an insignificant effect on temperature in a normal invididual, but cause a considerable drop in temperature of a fever patient. This action is stronger in antipyrine and the salicylic acid group than it is in quinine. But quinine is much preferable to these compounds or in fact any other substance known at present, as a specific against malaria.

Metabolism as measured by the nitrogen excretion is at first increased by quinine and then often considerably diminished. In fact it is always largely diminished after large doses. Quinine is for the greater part destroyed in the organism if ingested in moderately small quantities. Giemsa and Schaumann[1] state that the power of the organism in destroying quinine is increased with repeated dosage with the substance. Schmitz,[2] however, was unable to confirm this statement.

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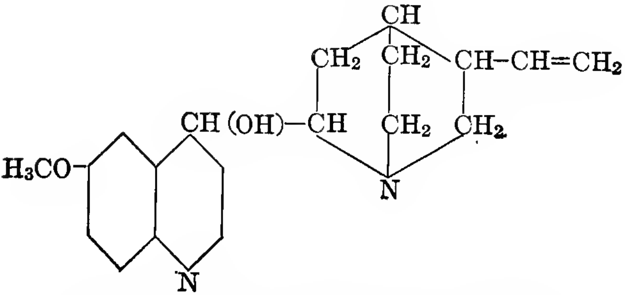
[1] Giemsa and Schaumann, Arch. Schiffs. Tropen hyg., **11**, Vol. III (1907).

[2] Schmitz, Arch. exp. Path. Pharm., **56**, 301 (1907).

The constitution of quinine can be to-day regarded with a considerable degree of certainty as being formula (I).[1] The side chain of the para-methoxy-quinoline that contains a piperidine ring is designated as the loipone or meroquinine part of the formula. Of the accompanying alkaloids cinchonine (III) stands very near to quinine, since it lacks only the methoxy group in the para position. But this very slight chemical difference reduces the effectiveness of the physiological action tremendously. Cinchonine is more detrimental to the heart, and possesses a cramp-excitant effect that is only very slightly apparent in quinine. Moreover cinchonine is a much less efficient febrifuge, and its specific action against malaria is only vaguely apparent, and only after large doses. But it seems to be clear that the secret of the action of the methoxyl group lies in the covered hydroxyl group, because the higher alkyl derivatives obtained from cupreine (II) such as quinethyline, quinpropyline, quinamyline have an action still more powerful than that of quinine. In other words, the more readily oxidizable is the alkyl group which covers the hydroxyl, the more powerful is

I QUININE



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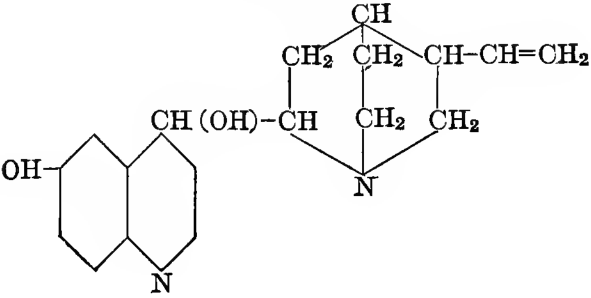
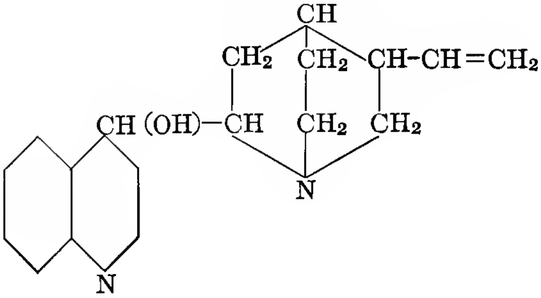
[1] Compare Rabe, Ber., **40**, 3655 (1907); **41**, 62 (1908).

the action of the compound[1] on account of the greater ease with which it is split down to cupreine.

II Cupreine



III Cinchonine



It seems, then, very probable that the slight febrifuge effect of cinchonine may not belong to that substance itself, but is due to cupreine, which is formed within the organism by the hydroxylation of the cinchonine in para position. In fact we have many cases analogous to this.

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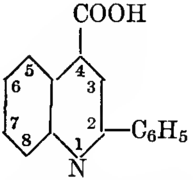
[1] Grimaux and Arnaud, Compt. rend., **112**, 766, 1364 (1891); **114**, 548, 672 (1892); **118**, 1803 (1894).

The earliest and most numerous investigations as to the connection between the effect of quinine and its constitution started from the quinoline part which was demonstrated to be present. At first there was assumed to be a tetra-hydroquinoline ring. Quinoline itself proved to be antiseptic, antizymotic and antipyretic in its effect. It was found to be weaker against fever than quinine and to be entirely useless against malaria. Moreover it caused some detrimental effects such as collapse and difficulty in respiration, even with the administration of small quantities.[1]

A recent quinoline derivative which deserves particular mention is Atophan, which is 2-phenyl-quinoline-4-carboxylic acid.



This substance has found practical application in acute attacks of gout because it causes an extraordinary increase in the elimination of uric acid. On account of the relation of quinine to quinoline, the derivatives of this latter body have been subjected to considerable physiological examination. Nicolaier and Dohrn[2] examined a series of the quinoline carboxylic acids, particularly in regard to their effect on uric acid excretion. From their results we may say that the 4 position for the carboxylic group is favorable; but the unsubstituted 4 carboxylic acid is without effect, as is also the 2-4 dicarboxylic acid. But if an aliphatic or aromatic radicle is introduced in the 2 position then the increased uric acid excretion is caused. This action is slight for the methyl-substituted body, but strong for the phenyl. Given this compound (atophan) the effect remains unchanged upon introduction of a second phenyl group (in 3 position), of a second carboxyl group (in 3 or 8 position), or of a methyl in 6 position, and hydroxyl weakens the effect. The exact behavior of atophan in the organism is as yet not fully understood. Very little of it is excreted unchanged. Moreover the increase in uric acid excretion cannot be ascribed to an increased nucleine destruction because the excretion of total nitrogen, phosphoric acid and sulphur is not increased. In fact the action would almost seem to indicate that the atophan releases an amount of uric acid which has been stored up in the organism, for after the discontinuance of the atophan treatment the uric acid excretion falls below the normal. The only other compound of those examined by Nicolaier and Dohrn which showed a similar action was 2-phenyl-3-oxyquinoline-4-carboxylic acid.

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[1] Donath, Ber., **14**, 178 (1881); Biach and Loimann, Virchow's Arch., **86**, 456 (1881); Brieger, Z. klin. Med., **4**, 296 (1882); v. Jacksch, Prager med. Wochschr., 1881, No. 28.

[2] Nicolaier and Dohrn, D. Arch. f. klin. Med., **93**, 331 (1908).

Isoquinoline is similar in every respect to quinoline.[1] When hydrogen of the quinoline is substituted by methyl groups the effect is weakened, but is qualitatively the same.[2] The introduction of methoxyl in the para position in quinoline weakens the antipyretic effect which is just the opposite of the action of the same group in the relation between cinchonine and quinine.[2] A considerably stronger antipyretic body is para-methoxy-tetra-hydroquinoline (Thalline) (I) whose effect, however, is of short duration. This substance is also injurious to the blood and kidneys.

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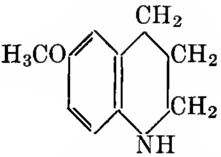
[1] Stockmann, J. Physiol., **15**, 245 (1894).

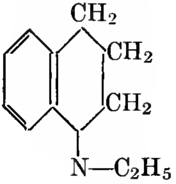
[2] Ibid.

I. Thalline

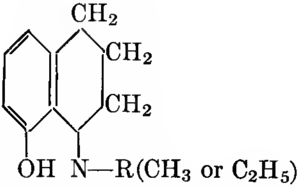


This effect is not altered either by the introduction of alkyl radicles, nor by the introduction of acid radicles in the imino group. A similar condition holds also with kairine (II) and kairoline (III) which are both preparations which are without a methoxyl group, and are alkylated on the nitrogen.

II. Kairine



III. Kairoline



None of these quinoline derivatives approaches the specific effect of quinine.

In the meroquinine residue of the quinine molecule the binding of the piperidine nitrogen by the bridge containing hydroxyl is of prime importance. If this is split off, as in the change from quinine to quinotoxine (IV), or in the same way if cinchonine is converted to cinchotoxine, these new substances do not behave as febrifuges at all, but as a digitoxine-like poison.[1] We are, however, hardly surprised by this toxic effect, when we note the presence of two groups of particularly great capacity for reaction—the CO and the NH groups.

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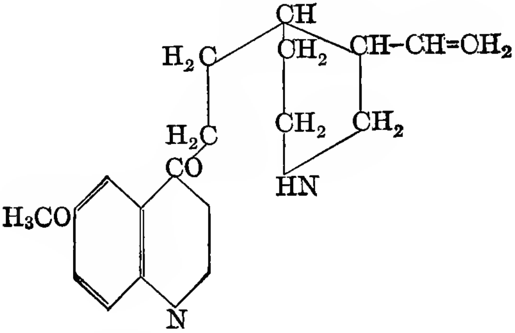
[1] v. Miller and Rohde, Ber., **33**, 3214 (1900).

The unsaturated side chain of the quinine seems to have a definite significance. If hydrogen is added at the double binding, the poison effect is hardly changed for mammals and infusoria. Hydrochlor-quinine, which is formed by addition of HCl, is said to be less poisonous for mammals than quinine, although it is more poisonous for certain infusoria.[1]

IV. QUINOTOXINE



In order to have a sort of standard test body that might stand as near as possible to the object of attack of the specific quinine effect, the malaria parasites, Tappeiner[2] selected the paramecium, and undertook experiments upon it. It was found that the order of strength in quinine effect is first para-methoxylepidine (V), then lepidine (VI), and finally quinoline; but that meroquinine (VII) is entirely without such effect.

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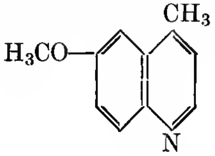
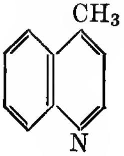
[1] Hunt, Arch. intern. pharmacodyn, **12**, 497 (1904).

[2] v. Tappeiner and Grethe, Deut. Arch. klin. Med., **56**, 189, 369 (1896).

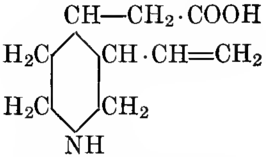
V. PARAMETHOXYLEPIDINE



VI. LEPIDINE

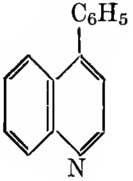


VII. MEROQUININE



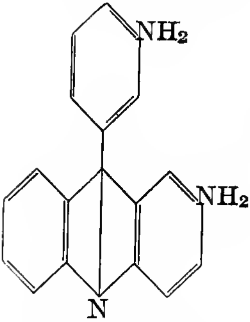
On the other hand γ-phenylquinoline (VIII) is considerably stronger in action than quinine.

VIII. γ-PHENYLQUINOLINE

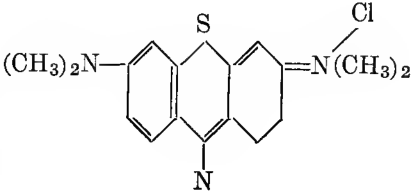


We may conclude, then, that the action of quinine upon infusoria proceeds from the quinoline ring, and can be materially increased by the complex attached to it in the γ position, even though this complex be in itself inactive. Since the substitution of the benzol ring proved to give such an effective compound it was natural that the phosphines, the beautifully colored compounds obtained from acridine, such as chrysaniline (IX), should be tested out. This was done, and they were found extraordinarily effective. But these substances, as well as phenyl-quinoline, do not seem to destroy the malarial parasites, but only to paralyze them in a manner similar to the constitutionally related methylene blue (X).[1]

IX. Chrysaniline

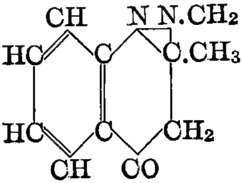


X. Methylene Blue



The constitution which Knorr first[2] ascribed to a tetra-hydroquinoline derivative was the cause for testing out the so-called dimethyl-oxy-quinizine (I) with a view to finding antipyretic effects, and such an effect was found to be very pronounced[3] and led to the name of this compound, Antipyrine.

I. Antipyrine



It was only later[4] that this compound was recognized

Mannaberg, Arch. klin. Med., **59**, 185 (1897).

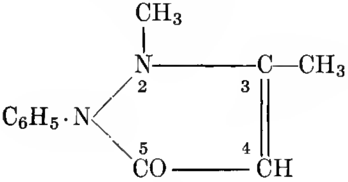
[2] Knorr, Ber., **17**, 546, 2032 (1884).

[3] Filehne, Z. klin. Med., **7**, vol. 6 (1884).

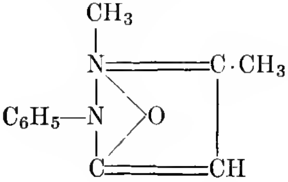
[4] Knorr, Ann. Chem., **238**, 137 (1887).

as dimethyl-phenyl-pyrazolon (II). Michaelis[1] affirms that the formula (III) can also be ascribed to this body.

II. Antipyrine



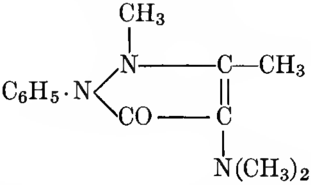
III. Antipyrine



Antipyrine does not act against malaria, but aside from this it is to be preferred over quinine, as it has less undesirable side effects, and it has a specific anti-neuralgic action.

The alkylation of the nitrogen is of importance. Phenyl-monomethylpyrazolon has no particular antipyretic action. The presence of the aromatic substituting group is, according to Curtius[2] not essential for the physiological action, but Filehne[3] finds that it is important for the degree of effect. The introduction of the tolyl group in place of the phenyl, giving us tolyl-pyrine, does not cause any essential change. A compound which is better than antipyrine in regard to strength and duration of effect is the 4-dimethyl-amino-antipyrine, which is called Pyramidon (IV).

IV. Pyramidon



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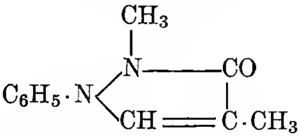
[1] Michaelis, Ann. Chem., **320**, 1 (1902).

[2] Curtius, Ber., **26**, 408 (1893).

[3] Filehne, Z. klin. Med., **32**, 568 (1907).

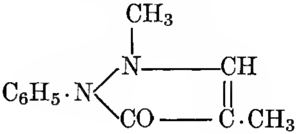
[3] Antipyrine (V) is considerably more poisonous than the ordinary antipyrine; but when we go to the dimethylamino derivatives we find the situation reversed.

V. [3] Antipyrine



Iso-antipyrine (VI) is, so far as toxicity is concerned, about like ordinary antipyrine.[1]

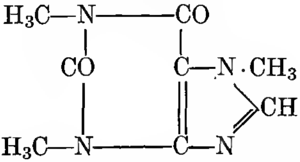
VI. Iso-antipyrine



The Purine Group

This group is important on account of the diuretic effect that is found in most of its members. The member of the group that was formerly of greatest therapeutic importance is caffeine (I). Associated with its diuretic action there is a stimulating effect upon the nervous system.

I. Caffeine



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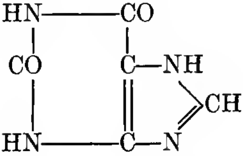
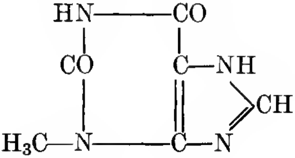
[1] Kobert, Z. klin. Med., **62**, 57 (1907).

Xanthine (II) has practically no diuretic effect. Of its monomethyl derivatives the 3-methyl xanthine (III) is more distinctly diuretic, and the 7-methyl-xanthine (heteroxanthine) (IV) is only insignificantly diuretic in action.

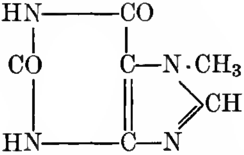
II. Xanthine



III. 3-Methyl Xanthine

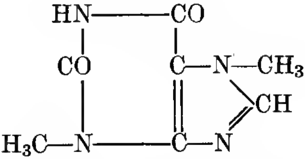


IV. Heteroxanthine



The dimethyl xanthines are more strongly diuretic than caffeine. Of these theobromine (V) is the least active, while theophylline (VI) and para-xanthine (VII) act more strongly.[1]

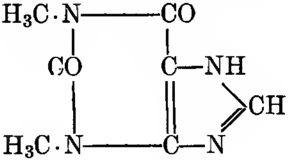
V. Theobromine



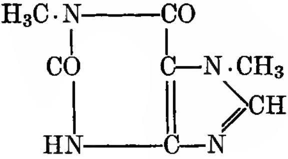
Theophylline (Theocine) is the most rapidly powerful of all in its action, but its effect diminishes very quickly.

[1] Arch. exp. Path. Pharm., **44**, 319 (1900).

VI. Theophylline (Theocine)



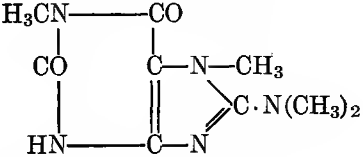
VII. Paraxanthine



It has been determined that the effect of theocine is due only to the closing of the imide-azol ring.[1] Ethyl-methyl-xanthine is similar in action to theobromine.[2] Other members of the group which also act as diuretics are ethyl-theobromine, ethyl-para-xanthine and ethyl-theophylline. Ethyl-theophylline is weaker than ethyl-theobromine.[3]

8-dimethyl-amino-para-xanthine (Paraxine) (VIII) acts very energetically and persistently but not instantly like theophylline.

VIII. Paraxine



[1] Dreser, Pflüger's Arch., **102**, 1 (1904).

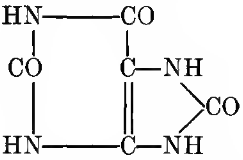
[2] Birk, Dissertation, Halle-Wittenburg, 1905.

[3] Bergall and Richter, Z. exp. Path., **1**, 655 (1905).

8-dimethyl-amino-heteroxanthine, on the other hand, like theophylline, acts intensely but only for a short time.[1]

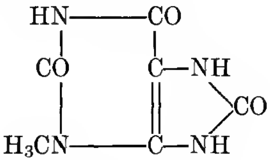
Uric acid (IX) is a diuretic according to Starkenstein,[2] but in large doses it injures the kidneys.

IX. Uric Acid

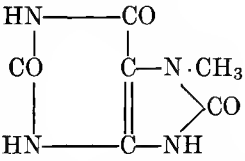


3- and 7-methyl uric acid (X), (XI), cause at first anuria, then a strong flow of urine.

X. 3-Methyl Uric Acid



XI. 7-Methyl Uric Acid



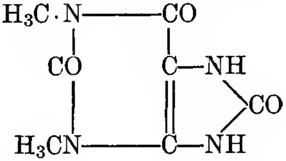
1-3 dimethyl uric acid (XII) has a slight diuretic action and is non-injurious. 1-3-7 trimethyl uric acid (hydroxy-caffeine) (XIII) is a strong diuretic and is also non-injurious at least in the case of rabbits.

---

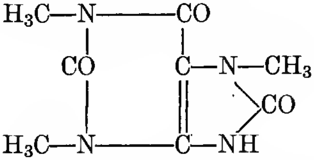
[1] Forschback and Weber, Arch. exp. Path. Pharm., **56**, 186 (1907).

[2] Starkenstein, Arch. exp. Path. Pharm., **57**, 27 (1907).

XII. 1-3 Dimethyl Uric Acid

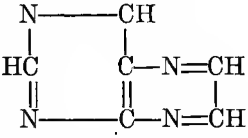


XIII. Hydroxy Caffeine



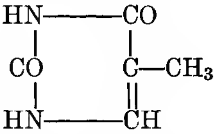
The derivatives of the closely related azinpurine (XIV) act as diuretics similarly to the purine derivatives; but they are distinguished from the latter in having a stronger cramp-excitant effect.[1]

XIV. Azinpurine



According to Levene[2] even thymine (XV) acts like the dimethyl and trimethyl xanthines.

XV. Thymine



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[1] Sachs and Meyerheim, Ber., **41**, 3959 (1908).

[2] Levene, Biochem. Zeitschr., **4**, 816 (1907).

Hydrazine, Its Derivatives, and Hydroxylamine

Hydrazine or diamide, $H_2N—NH_2$, is much more poisonous than ammonia.[1] Subcutaneous injection of the sulphate in quantities of 0.1 gm. per kg. of body-weight causes in the case of a dog, an excitation, then depression and finally coma. There occur irregularity of the pulse, vomiting, salivation and evacuation of the bowels. The quantity of allantoin in the urine, and possibly in the saliva is increased.

The entry of acid radicles into the molecule weakens both the chemical reactivity and the physiological activity. Dibenzoyl-diamide has, according to Borissow, a weaker action than diamide. Morevoer the action is manifested by somewhat different phenomena. The physiological action is also less in the case of semi-carbazide,

$$H_2N—CO—NH—NH_2,$$

and amino-guanidine,

$$H_2N—C(NH)—NH—NH_2;$$

but pyrocatechin-mono-carbonic acid-hydrazide,

$$HO—C_6H_4—O—CO—NH—NH_2$$

is said to act about like free hydrazine.[2]

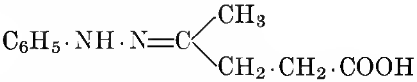
The derivatives of phenyl hydrazine were subjected to a great deal of investigation, because it was expected that among these compounds there might be found substitutes for antipyrine. The reason for this expectation was the constitutional formula which was originally ascribed to that valuable medicinal body—Antipyrine. Phenyl hydrazine itself is a powerful poison for all the tissues and for the coloring matter of the blood.[1]

---

[1] Loew, Ber., **23**, 3203 (1890); Borissow, Z. physiol. Chem., **19**, 499 (1894).

[2] Loew, Chem. Ztg., **22**, 349 (1898).

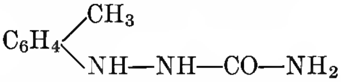
A strong febrifuge effect, but at the same time a strong toxic effect, were found for the mono-acetyl compound $C_6N_5 \cdot NH \cdot NH \cdot CO \cdot CH_3$ (hydracetine),[2] and for the diacetyl compound. The diacetyl body is weaker in action than the monacetyl derivative. Similar effects were observed with phenyl hydrazine-levulinic acid, which was called Anti-thermine,



$$C_6H_5 \cdot NH \cdot N{=}C \left\langle \begin{matrix} CH_3 \\ CH_2 \cdot CH_2 \cdot COOH \end{matrix} \right.$$

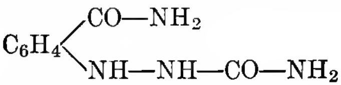
according to Nicot,[3] and monobenzoyl hydrazine.[4]

Several aromatic semicarbazides seem to be more fitted for therapeutic use, because they have less side effects, and they have a distinct anti-thermic action.[5] Two such bodies which were particularly recommended were carbaminic-acid-metatolylhydrazide (Maretine),[6]



$$C_6H_4 \left\langle \begin{matrix} CH_3 \\ NH—NH—CO—NH_2 \end{matrix} \right.$$

and metabenzamido-semicarbazide (Cryogenine).[7]



$$C_6H_4 \left\langle \begin{matrix} CO—NH_2 \\ NH—NH—CO—NH_2 \end{matrix} \right.$$

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[1] Hoppe-Seyler, Z. physiol. Chem., **9**, 34 (1885).

[2] Guttman, Berl. klin. Wochschr., **26**, 437 (1889).

[3] Nicot, Nouv. Remedes, 1887.

[4] Heinz, Berl. klin. Wochschr., **27**, No. 3 (1890); Virchow's Arch., **122**, 114 (1890).

[5] Lumière and Chevrotier, Compt. rend., **135**, 187 (1902).

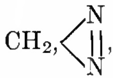
[6] Barjansky, Berl. klin. Wochschr., **41**, 607 (1904).

[7] Lumière and Chaumier, Nouv. Remedes, **19**, 289 (1902).

Hydroxylamine is similar to hydrazine, not only chemically, but also physiologically. Like hydrazine it exhibits a strong toxic action and destroys the coloring matter of the blood.[1] Binz[2] attempted to ascribe the effect in part to the formation of nitrites, but this contention was refuted by Loew.[3] There is on record one case of poisoning by phenyl hydroxylamine.[4]

The aldoximes exhibit, according to Bonfred,[5] the combined effect of the corresponding aldehydes and nitrites. This effect is probably produced by oxidation of the oximido group which is split off.

Derivatives of Hyponitrous Acid

Diazomethane  $CH_2,\!<\!\begin{array}{c}N\\ \|\\ N\end{array}$, is an exceedingly poisonous gas.[6] It causes difficulty in breathing, pains in the chest, and general depression. According to Jaffe[7] the aromatic azo compounds are also poisonous, because of the ease with which they split off gaseous nitrogen. Diazobenzol causes hæmoglobinuria.[8] Azo dyes are in general not poisonous for mammals. A number of dyes derived from benzidine have proved to be effective against certain animal parasites (trypanosomes).[9] These bodies are combinations of tetra-azotized benzidine or its ortho-sulphonic acid, or its ortho-dichlor compound with two molecules of 2-amino-naphthaline-3-6-disulphonic acid (Trypan red) or with other naphthaline 3-6-disulphonic acids. According to Ehrlich[1] other radicles can be introduced into these bodies, preferably in the 7 position. Combinations with 1-8-amino-naphthol-3-6 disulphonic acid are also effective against certain trypanosomes.[2]

---

[1] Raimundi and Bertoni, Gaz. chim. ital., **12**, 199 (1882).

[2] Binz, Arch. exp. Path. Pharm., **36**, 403 (1895).

[3] Loew, Ber., **23**, 3206 (1890).

[4] Lewin, Arch. exp. Path. Pharm., **35**, 401 (1895).

[5] Fränkel, Arzneimittelsynthese, 2d Ed., pp. 72–73.

[6] v. Pechmann, Ber., **27**, 1888 (1894).

[7] Jaffe, Arch. exp. Path. Pharm., **35**, 413 (1895).

[8] Baumann and Herter, Z. physiol. Chem., **1**, 267 (1877).

[9] Ehrlich and Shiga, Berl. klin. Wochschr., **41**, No. 13–14 (1904).

Azoimide is less poisonous for plants than either hydrazine or hydroxylamine. But for mammals it causes lightning-like cramps and sometimes immediate death, with a dark coloring of the blood.[3] Loew attributes the effect to a reaction of the sudden breaking down of the protoplasm.

RÉSUMÉ

A brief review of our discussion of the organic compounds may now be profitable. We have studied certain groupings which furnish the preliminary basis for certain effects. Then we have observed that, given these fundamental nuclei, the physiological action of the compounds may be varied—either weakened or strengthened or modified by the action of individual side chains. Among those side chains which seem to release the latent action of the nucleus we find those groups which also favor an increased chemical activity. The strikingly noticeable groups of this sort are the amino, hydroxyl and carbonyl groups. In fact these groups are so powerful in this manner that it is frequently necessary to introduce other groups with a weakening effect before the compound is suitable for safe and reliable therapeutic use. Such a weakening of action may naturally be produced upon amino bodies by introducing acid constituents. A possibility which is to be guarded against is the carrying of this weakening effect so far as to destroy the action entirely. Such is often the case with carboxylic acids and even more frequently with sulphonic acids. This is easily understood from a chemical standpoint, because we have strongly acid groups introduced into basic compounds and we should expect this to wholly change the character of the compound. But this same phenomenon is also observed in the case of compounds which are already of an acid nature such as phenols. In such cases we should expect an increase rather than a decrease of effect upon introducing an acid radicle. We are, however, reasonably certain in saying that in this case there is another factor which plays a very large part. This factor is the distribution coefficient. The carboxylic acids and sulphonic acids must of course enter the body fluids in the form of their alkali salts, and these substances are not nearly so easily taken up by the tissue cells as are the free phenols.

---

[1] Ehrlich, Berl. klin. Wochschr., **44**, No. 9–12 (1907).

[2] Nicolle and Mesnil, Ann. inst. Pasteur, **20**, 417, 513 (1906).

[3] Loew, Ber., **24**, 2947 (1891).

The alkyls we found to play an important rôle in several ways. In the first place, we repeatedly observed that their accumulation about certain groups is a condition for sleep-producing effects. The alkyl groups also have a specific action when combined to the ring by means of oxygen, thus acting as closures for hydroxyl or carboxyl groups. In the case of hydroxyl groups their function is frequently a softening of the otherwise violent reaction. In the case of carboxyl groups their effect is generally in the nature of a neutralization of the disturbing effect of violent action. The alkoxyl group occasionally also strengthens an effect; but such action is probably explicable in most cases by a change in the distribution coefficient.

Although in general the alkyl groups are about the same in effect, yet in some cases there are decided differences. This is particularly noticeable in the case of the sleep-producing compounds. In fact in this respect special action was for some time assigned to the ethyl group. But more recent observations have shown that the propyl groups are at least the equal if not superior to the ethyl. This seems to be the case with some series where equivalence of all alkyl radicles was assumed merely from an observation and comparison of the methyl and ethyl compounds. Thus, according to Stürmer and Lüders [1] the propyl ester of para-amino benzoic acid (Propæsin) is essentially more active than the corresponding ethyl ester (Anæsthesin).

An a priori opinion, that is only too readily conceived, is that the combination of several substances which act in a similar direction will result in an especially desirable action. But this has often led to disillusionment and failure. Examples of such failures we noted in the combinations of salicylic acid with other febrifuges. More recently Stürmer and Lüders [2] report a fact which appeared, to them at least, to be very striking—namely that the esters of para-amino benzoic acid with phenols and hydroaromatic alcohols (as guaiacol, thymol, menthol), which in themselves have an anæsthetic action, are really weaker in effect than the corresponding compounds of aliphatic alcohols. There may be several reasons for this. In the first place it is likely that such compounds can act only in the form of their decomposition products. This splitting up proceeds only with difficulty, as is generally the case for these salicylic acid compounds. Then, too, it may be that in

[1] Stürmer and Lüders, Deut. med. Wochschr., 34, 2310 (1908).

[2] Ibid.

order to be effective, both components must find anchorage at the same point. If such were the case it is quite possible that the physiologically less active component may hold off or stand in the way of the more active one. Even in cases where the effects of the components do seem to be additive in a positive manner, there still remains to be decided by experimentation in each individual case, whether the proportion of the two which holds in a chemical combination is that proportion which gives the best physiological results. Therefore we must confess that work which looks toward a synthesis of such compounds is in general not a promising field.

It will of course be understood that this treatise has not attempted to refer to all the observations which are relevant to the subject. Only the most important and most thoroughly investigated groups have been considered. We have not touched upon the interesting subject of the effect of constitution upon the odor and taste of chemical compounds. Those who are interested in this subject we would refer to the writings of Zwaardemaker, "Die Physiologie des Geruchs," translated by Junker von Landegg.

Unfortunately, experimentation in this field must suffer, among other things, from the considerable influence of the subjectivity of the observer. For example, opinions are wholly contradictory whether *p*-anisol-carbamide has a sweet taste like the corresponding phenetol derivative or not. We must also remind our readers of the complete work of Fränkel, "Die Artzneimittelsynthese auf Grundlage der Beziehungen zwischen Chemischem Aufbau und Wirkung, 2. Aufl., Berlin, 1906, a work which has served largely as a guide for the older literature.

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